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THE STATISTICAL ORGANIZATION OF NERVOUS ACTIVITY*

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INTRODUCTION

THIS IS NOT a review of neurophysiology but a synopsis of some theories which may lead to an understanding of the mental aspects of nervous activity, namely ideas and purposes. The highway to ideas lies through statistical conceptions from their logical foundation in Boolean algebra through modern methods of constructing invariants by averaging over groups of transformations. Purposive behavior depends upon how output affects input which, in turn, depends upon a nervous system whose organization can be treated statistically. This is instanced in one reflex. Known details of other mechanisms are in current publications. The theory is extremely atomistic. The ultimate units of nervous activity are impulses which, being all-or-none signals, submit to the Boolean algebra of propositions and hence to statistical treatment. A field-theory does not now exist and may never cope with the inherent complexities. It has been shown to be unnecessary.

Figure 1 shows a neuron, and labels the *dendrites*, *cell-body* and *axon*. Proper irritation of the cell starts off a signal, a ring of negative voltage, which then travels from the body along the axon and its branches at a speed between one foot and three hundred feet per second, depending upon the thickness of the axon. The thicker axons are also longer, so that the total time of transit is more nearly the same from the beginning

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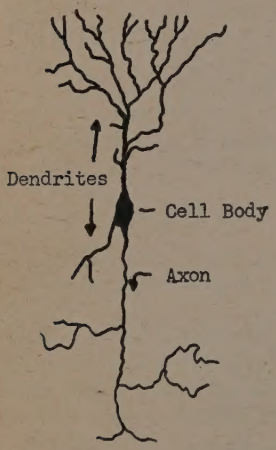
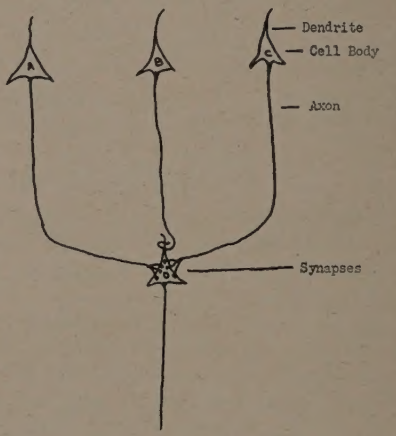
†John Simon Guggenheim Fellow for 1947.

to end of any axon than if all were of one diameter. We shall treat this time as if it were constant, and therefore negligible. The end of an axon is either in a muscle or gland, or else forms a small knob on another neuron, as in Figure 2. These knobs are called *synapses*. Signals arriving at synapses irritate the recipient neuron locally for about two-tenths of a millisecond. If signals arrive within that time on enough of its synapses, they combine to start off a signal half a millisecond later along the axon of the recipient neuron. The amount of irritation required for



Real Neuron (one type)

FIGURE 1



Conventional Neurons.

FIGURE 2

this is called the *threshold* of the neuron, and the delay the *synaptic delay*. After transmitting one signal, a neuron will not transmit another for about eight-tenths of a millisecond: it is said to be *refractory*. It is obvious from this that no two successive signals along the same axon can combine their irritation at the terminal synapse. Although the anatomy is not known, impulses arriving somewhere in the vicinity of a neuron, either directly or by way of sub-threshold irritation of intermediary neurons, do prevent the neuron in question from responding to otherwise adequate irritation. We draw such an inhibitory ending as a loop around a dendrite, as in Figure 2. Neurons are unlike ordinary

electric circuits in that the energy sustaining the signal is always supplied locally; that is why its final size is not affected by events at its origin or along its course. Neurons have other properties which we shall ignore in the present sketch.

Let time flow equally in measured lapses, say a millisecond apiece, and number them beginning with any one that is convenient. A given neuron cannot transmit two signals in a single lapse: it must have either one on it or none. For every such lapse there is therefore one proposition, say $S_A(t)$ for neuron A, such that knowledge of its truth or falsity describes the neuron completely—namely, $S_A(t)$ asserts that there is a signal on A at t. Further, since neurons influence one another only by signals, all the significant relations within a nervous net can be expressed as propositional relations which only involve truth-values. This is to say that nervous activity can be described in the calculus of propositions as follows. If, for two propositions p and q, we use the notations:

$$\sim p = \text{'}p \text{ is false', 'not } p\text{'}$$

$$p + q = \text{'either } p \text{ or } q \text{ or both'}$$

$$p \cdot q = \text{'both } p \text{ and } q\text{'}$$

$$p \supset q = \text{'if } p \text{ then } q\text{', '}p \text{ implies } q\text{'}$$

$$p \equiv q = \text{'}p \text{ if and only if } q\text{'},$$

then possible relations between the actions of neurons in Figure 2 will include the cases:

1). Simultaneous summation from both A and C is necessary to to excite D:

$$S_D(t + 1) \equiv S_A(t) \cdot S_C(t).$$

2). Either A or C is alone capable of exciting D:

$$S_D(t + 1) \equiv S_A(t) + S_C(t).$$

3). A can excite D, unless B inhibits it:

$$S_D(t + 1) \equiv S_A(t) \cdot \sim S_B(t).$$

In the whole nervous net we shall have an equivalence of this kind defining the conditions of excitation for each neuron in the net. Provided the net is free of circular paths—that is, if it is never possible to follow down the axon of a neuron and its successors in such a way as to return to the starting point—then these equivalences may be substituted into one

another so as to obtain, for each output-neuron, a set of necessary and sufficient conditions of excitation, in the form prescribed by this calculus, in terms of the signals coming into the system as input from sense-organs. If we are allowed extra delay between input and output, we can construct a net to make the output any desired logical function of the input, provided only it satisfy the condition that it is false when all its atomic components asserting the occurrence of signals in the input are false. For if no signals ever enter the net, none can emerge. If spontaneously active neurons are admitted, this restriction also vanishes.

If neurons successively excite one another in a circle, a signal once started can circulate through the net indefinitely. Among other things, such circuits introduce the universal and existential operators of logic, applied to time past. They constitute a memory of a kind, whereby, in principle, signals delivered once to a net may cause it to behave differently to certain inputs forever after. The actual durability of learning requires more stable devices than this, amounting to a change in the connections of the net: but this may not come formally to anything very different. To make marks and read them later also brings consequences formally similar to circulating activity in the net.

Besides these microscopic properties, the ten billion neurons in the brain show regularities in the large which are properly statistical, and are necessary for a nervous system to survive and reproduce.

One kind extracts the important universals out of the excessive particularity of their exemplars. An animal must recognize visible objects irrespective of his distance from them and his perspective—that is, independent of their absolute size or position in the visual field. The latter invariance he secures by a reflex which snaps the eyes to the "center of brightness", and the image therewith to a standard place. This is one general kind of mechanism. A second secures the size-invariance of shapes: the nervous system may actually form all the possible magnifications and constrictions of the image, either simultaneously at different places or successively at one place, calculate an important parameter for each size, and add them. Such a sum would have been the same, by definition, if we had started with the same shape in a different size. Enough invariant sums of this kind may be computed to enable the system to recognize the form as well as it needs to. Since, in a finite net the number of such transformations is finite, these sums are really averages over groups of transformations.[1]

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[1]Mechanisms differ from one another in the calculation of parameters to be averaged. Thus, in effect, the reflex that centers gaze on objects to be recognized, by moving the eye so rapidly as to flush the visual cortex with "ons" and "offs", assigns there the value zero to all translations except the last,

Another statistical principle of organization occurs wherever the nervous system, built on all-or-none principles, has to deal with the important variables in the physical world that are continuous along one or several dimensions. Light varies continuously in intensity, hue and shade; sound, in loudness and pitch; and so on. The nervous system represents these magnitudes as averages of many kinds. It averages over time when a sense-receptor emits a series of impulses whose *frequency* measures the intensity of the continuous variable stimulating it, or when a muscle fiber in tetanus adds increments of tension evoked by signals along the innervating axon during some time past. It likewise averages in space when a higher grade of a sensory variable stimulates more receptors, or more motor axons excite more fibers in a muscle. This is one reason for the enormous reduplication of parallel paths in the nervous system. The result of all this averaging is a very fair approximation to a continuous dynamical control-system for gaging the application of physical force to move matter in the light of continuous information about the consequences.

These matters are well illustrated in the simple case of the stretch-reflex. With some simplification the mechanism is diagrammed in Figure 3. Receptors in the muscle send signals into the spinal cord at a frequency ρ which is some monotonic function $f(L)$ of the length of the muscle. These signals are reduplicated in branches of the sensory axons carrying them, to converge on the motor cells of the ventral horn which innervate the same muscle. The motor neuron will transmit a signal whenever the number of afferent signals coinciding on it within a short interval exceeds the threshold h. We shall take this interval as the unit of time. If afferent impulses are statistically independent and asynchronous, the probability-distribution of the total number arriving per unit time will tend either to the Gaussian or the Poisson distribution, depending upon the magnitude of ρ. In the former case, if N be the average number of different axons afferent to one motor neuron, the mean will be $N\rho$ and the variance $N\rho(1 - \rho)$, so that the average number of signals per unit time delivered to the muscle along a motor axon will be

$$E(\rho) = erf\left[\frac{h' - \rho}{(\rho(1 - \rho))^{1/2}} N^{1/2}\right],$$

$$erf(x) = \frac{1}{(2\pi)^{1/2}} \int_x^\infty e^{-(x^2/2)}\, dx,$$

which therefore alone determines the average. We can not conceive any mechanism for detecting universals which may not be described in this general manner of averaging over groups.

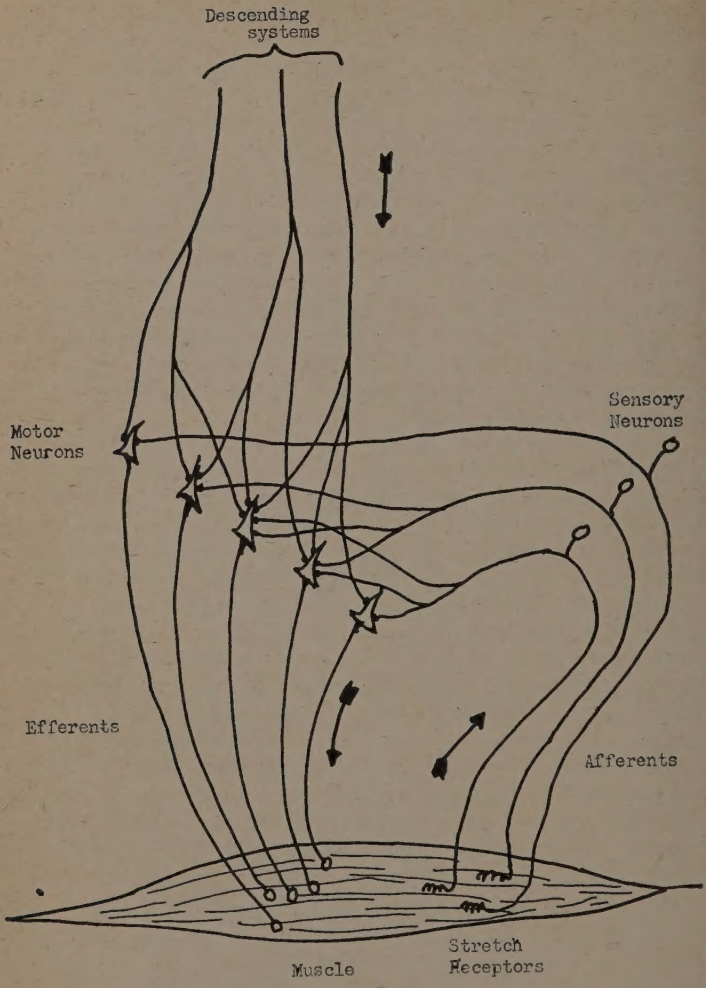
Descending systems
Motor Neurons
Sensory Neurons
Efferents
Afferents
Muscle
Stretch Receptors

FIGURE 3

in which $h' = h/N$, the relative threshold. $E(\rho)$ is sigmoid, monotonic, and varies from zero to unity as ρ does, provided that $h' < 1$.[2] We see that the inflection point of $E(\rho)$ is reached as ρ reaches the relative threshold h', and that its slope at that point is proportional to the square-root of N. This mean frequency $E(\rho)$, delivered over the axons innervating the muscle, will develop a tension given by a certain monotonic function $T = T(E)$, which then tends to reduce the length of the muscle. This familiar process, whereby a change in the output causes a change of opposite sign in the input, sets equilibrium length L and a tension T which just holds that length against the external load. It also returns the muscle to that length if it be perturbed from without in any way.

It is evident that the equilibrium length sought by the reflex under given circumstances can be varied at will by controlling the value of the central threshold h'. Formally, this is exactly the effect wrought by additional signals descending from higher nervous structures to intervene in the stretch-reflex arc. The engineer would say that the signals from higher structures control the gain around the loop of the stretch-reflex. Quite generally, this is the plan of sub- and super-ordination prevailing in the nervous system. No higher structure alone can move muscles: it can only control the "central amplification" of the elementary spinal reflex arc. In monkeys, to cut off all the afferents from a limb acutely paralyzes it as completely as if the motor nerve had been severed.

Three or four principal circuits send parallel descending tracts to control the spinal cord in this way. Some of them proceed from their own sensory afferents and in turn have their own gains controlled by super-ordinate systems. Thus the labyrinths inform the vestibulospinal circuit which direction is down, whereupon it amplifies the stretch-reflex in the anti-gravity muscles accordingly. Similar circuits control the velocity of movement, to keep it smooth and in constant relation to moving physical objects. Others keep the body at even temperature, the blood pressure constant, and the respiration sufficient to hold the carbon dioxide and oxygen tensions at proper values. Many of them are regularly periodic, like those of walking, breathing and sleeping.

There are circuits that pass from the central nervous system through

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[2]Actually, numerous complications beset this simple line of argument. Refractoriness causes $E(\rho)$ to level off at an asymptote short of unity, and inhibitory impulses arrive from antagonistic muscles, "associative" neurons in the spinal cord and higher structures. Lloyd's facilitation and inhibition at this synaps must likewise be included. Even so, the great generality of reasoning based on the limit-theorem of Laplace and Liapunoff permits us to take such influences into account in the same way. The resulting function is provisionally concordant with the pitifully few $E(\rho)$ curves in the physiological literature.

effectors into the world about us to procure the necessities of life: and, of them, some, making use of symbols, keep us adjusted to the complication of society. When two are incompatible, choice is insured either by one inhibiting the other or by a requirement of summation from the rejected to the preferred. Since, of three such circuits, the first may dominate the second, the second the third and the third the first, values need have no common measure. When these circuits are built into us by the usual processes of growth, they operate so automatically that we are scarcely aware of them. Experience of choice usually arises at the moment we are forced to make a novel decision.

At present we do not know how our nets are changed by such decision. We try many things and finally succeed; the successful mode of action most commonly becomes the preferred: but whether this is due to growth of neurons or changes in threshold is obscure. Heredity cannot fix the thresholds and connections of so many neurons. It can only lay down the general plan and leave particulars to chance. Experience brings order into this chaos, and in doing so gives us a memory unlike a written record. It is better conceived as the establishment of a connection, which, once made, works henceforth so that the new is always built upon the old. This gradual ordering of the nervous system is like permanent magnetization in an originally unmagnetic bar of steel. Apart from learning, a mathematical account of nervous systems whose connections are random in detail is part of the difficult and incomplete realm of statistical mechanics that deals with change of state. Even so, numerous calculations of quantities measured in experimental electrophysiology have been made, and there is reason to expect more in the near future.

We can summarize our conclusions as follows:

1) The actions of neurons and their mutual relations can be described by the calculus of propositions subscripted for time.

2) The nervous system as a whole is ordered and operated on statistical principles. Thereby it adjusts the all-or-none laws governing its elements to a physical world of continuous variation.

3) It detects universals.

4) It conserves its own level of activity, the condition of the body it inhabits, and its relation to the physical world by activity in closed paths such that a change in its output causes a change of opposite sign in its input.

5) It chooses between ends.
6) It alters its structure by experience.

Finally, the mathematical treatment of its activity presents numerous problems in the theory of probability and stochastic processes.

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EXPERIMENTAL DESIGN IN COMPARISON OF ALLERGENS ON CATTLE

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Tuberculosis and Johne's disease in cattle may be diagnosed by the injection into the skin of appropriate allergens (tuberculin and johnin) prepared from cultures of the organisms which cause these diseases. Animals which are or have been diseased show a reaction to the allergens in the form of a thickening of the skin immediately surrounding the site of injection. Unfortunately, when using current preparations of the allergens, cows with tuberculosis may exhibit some reaction to johnin, and vice versa. Even though the intensity of reaction is greater to the allergen of the disease from which the animal is suffering, some confuson in diagnosis results. The Pathological Division of the Bureau of Animal Industry has been carrying out studies which have as their purpose the development of allergen preparations more specific for each disease, and at the same time potent. The general results of these studies will be published elsewhere, but certain points relative to the experimental designs may be summarized here.[1]

In the experimental work on this problem, animals artificially sensitized to either tuberculin or johnin have been employed. The intensity of reaction to the allergen preparations may be measured by the amount of skin thickening produced using the technique of Dr. H. W. Johnson of the Bureau (1944). In preliminary tests it was found that a satisfactory degree of reaction to the allergen and a satisfactory measurement of the skin thickening could be obtained on the neck-flank, back and upper and lower side regions of the sensitized animals (Figure 1). Further, a total of 50 to 100 separate injections could be distributed over these regions, with reactions to the individual injections occurring independently.

Before starting the experimental program proper, the importance of various factors which might affect the response to allergens was studied in a series of uniformity trials. To illustrate the major findings, data from one of these trials is cited. Here a preparation of johnin was injected into johnin-sensitized cows. The material was administered at two concentrations in each of four regions (Figure 1) on each side of five cows. Summarized results and analysis are given in Tables 1, 2, and 3.

[1]The material is taken from notes on the consulting work done by the Experimental Design Committee of the U.S.D.A. in connection with the project.

TABLE 1
AVERAGE REACTIONS IN MM. (COWS AND CONCENTRATIONS)

	Cow No.					
Concentration	1	2	3	4	5	Average
1/100	6.72	10.97	10.84	7.72	6.88	8.63
1/1000	3.19	5.12	5.28	2.91	3.53	4.01

TABLE 2
AVERAGE REACTIONS IN MM. (BODY REGIONS AND CONCENTRATIONS)

	Region				
Concentration	Back	Neck-Flank	Upper Side	Lower Side	Average
1/100	5.78	10.95	8.40	9.38	8.63
1/1000	3.20	5.10	3.58	4.15	4.01

TABLE 3
ANALYSIS OF VARIANCE OF REACTIONS

Source of variation	Degrees of freedom	Mean square
Cows	4	40.60
Regions	3	43.81
Concentrations	1	426.66
Interactions		
Cow × region	12	5.15
Cow × conc.	4	5.24
Conc. × reg.	3	10.17
Cow × conc. × reg.	12	4.79
Sides	1	11.44
Interaction, cow × side	4	7.87
Other interactions with side	35	1.72

The reactions in this trial were unusually high, but otherwise the findings illustrate the conditions to be encountered. Of particular importance were the marked differences between cows and between regions. These differences were consistent from trial to trial, the back region giving low reactions, the neck-flank region high reactions, and the side regions average reactions (Figure 1). Reactions within a region were fairly homogeneous. The effect of varying the allergen concentration was here, and in the other trials, very pronounced relative to experimental error. A tendency to interaction of concentration and region was present in this trial, but its magnitude in the remaining uniformity trials led to the conclusion that failure to consider it in the design and analysis of the experiments would not lead to erroneous interpretations.

The cow by concentration interaction was here negligible, but estimates made from the series of experiments indicated that it was a small source of experimental error. Side variation was here not significant, and the results of the whole series of trials warranted the assumption that the left and right sides do not differ in response.

It will be noted in Tables 1 and 2 that a ten-fold dilution approximately halves the response, suggesting that the response is not a linear function of concentration. This relation was studied further in the other uniformity trials using series of concentrations, and it was found to be definitely curvilinear. It became essentially linear over a wide range, however, when logarithms of concentration were employed. Although not illustrated here, it was also learned in the series of uniformity trials that operators differed but little and that measurement errors were relatively small as compared to other sources of experimental error.

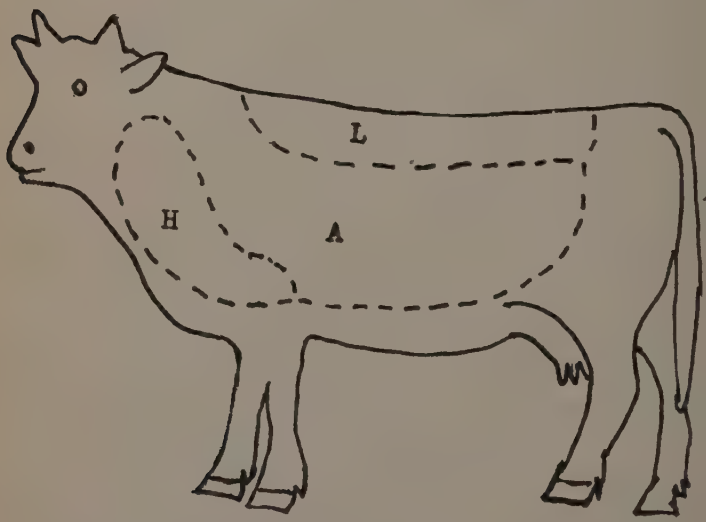

FIG. 1. Diagram of cow showing approximately regions found of higher (H), lower (L), and average (A) sensitivity. (Tracing from rubber stamp cow used by B.A.I. on data sheets).

These results indicated that a practical minimum for experimental error could be obtained if comparisons of allergen preparations were made on an intra-cow, intra-region basis, it being noted that comparable regions on the left and right sides of a cow may be considered as a single region.

The experimental program involved the comparison of numerous allergen preparations. In order that potency may be properly assessed and specificity ascertained, at least two concentrations of each preparation must be administered. As few as two concentrations may be used, however, only when the preparations being compared are known to be qualitatively similar and the potency of each is already approximately known. When faced with uncertainty as to qualitative similarity and potency as well, three, four or even more concentrations of each preparation may be required in order to obtain the desired information.

Usually, each of the four regions on a given side of a cow will furnish 8 to 12 usable injection sites, although less than this number may sometimes be available. Combining comparable regions on the two sides would thus yield homogeneous blocks with 16 to 24 injection sites. If the numbers of preparation-concentration combinations to be tested do not exceed 16 to 24, there might be employed a design of the randomized "complete" blocks type, in which all treatments occur in all regions. This would yield a minimum experimental error. On the other hand, the number of preparations and concentrations desired may require more injection sites than are available in a region. The use of a "complete" blocks design would then necessitate that the blocks overlap two or more regions, with an accompanying increase in experimental error. The increase in block size and, therefore, in error might be avoided by the use of an "incomplete" blocks design. In such a design only a part of the treatments are compared in each region, the particular set of treatments compared being different in each region. A "balanced incomplete" blocks design is to be preferred for the present purposes, since equal variance for all treatment contrasts is highly desirable, and computational complexities are avoided in the analysis. A balanced design is characterized by the occurrence somewhere within a block of every pair of treatments the same number of times. In the experimental program, experiments of both the "complete" and "incomplete" blocks type were used. An illustration of each is discussed in the following paragraphs.

A COMPLETE BLOCKS DESIGN

In this experiment a standard tuberculin preparation was compared

with a modified form. Three concentrations (250, 25 and 2½ parts per 10,000) of each were used; thus 6 treatments were studied. Fourteen replications were made on each of 5 cows, each replication falling within one of the regions of varying sensitivity. Treatment averages were computed for each cow, and the analysis shown in Table 4 was then conducted on the resulting 30 means (6 treatments on each of 5 cows). Measurements of skin thickness were recorded in millimeters (mm.).

TABLE 4
ANALYSIS OF VARIANCE, STANDARD VS. MODIFIED TUBERCULIN

	Degrees of freedom	Mean square
Between cows	4	4.11
Between treatments	5	26.34
Cow × treatment (error)	20	0.27

The basis for comparison of two materials is the ratio of concentrations required for the same effect. If one substance requires twice the concentration of another substance, it is only half as good. Bliss and Marks (1939) have discussed, with references, the biological assay method appropriate to studies in which response is a linear function of the logarithm of concentration. In this method, the ratio of concentrations required for a given effect is determined as the difference of log-concentrations. Geometrically this is the horizontal distance between the regressions of response on log-concentration for two materials being compared (Figure 2). If concentrations have been selected so that the differences between the logarithms of successive concentrations are constant, and if the regressions are linear and parallel, the estimation of relative potency is quite simple.

The tests for linearity and parallelism following the scheme of Bliss and Marks are shown for the present study in Table 5. This scheme divides the sum of squares for treatments in Table 4 (5×26.34) into 5 independent parts which are associated with the 5 effects listed in the lower part of the left hand column of Table 5. The figures in the "total reactions" row are simply the sums of the individual cow averages for each treatment. The figures in the "net sum" column are the sums of products of the "total reactions" and the corresponding coefficients in their respective columns. For example, the net sum for "Between materials" is

$$(-1)(29.24) + (-1)(15.08) + (-1)(5.57) + (1)(33.77) + (1)(19.03) + (1)(7.05) = 9.96.$$

The "Divisors" are obtained by multiplying the sum of squares of the coefficients in the corresponding row by the number of figures added to obtain the total reactions. For example, the divisor for "Between materials" is

$$5\{(-1)^2 + (-1)^2 + (-1)^2 + (1)^2 + (1)^2 + (1)^2\} = 30$$

The figures in the "S.S." (sum of squares) column are derived as (net sum)^2/divisor. These are also mean squares since each has but one degree of freedom associated with it. As a computational check, it should be noted that, except for rounding errors, these sums of squares total to the treatment sum of squares in Table 4 (5×26.34).

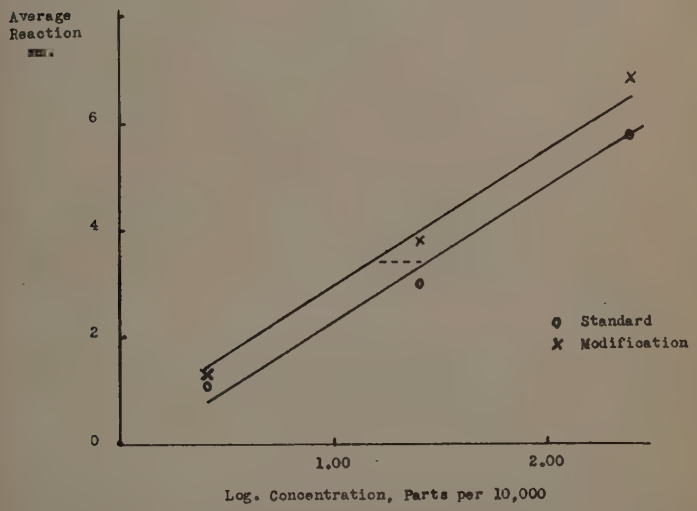

FIG. 2.– Common-slope regression lines fitted to data used in Tables IV and V. Log of potency ratio is represented by dotted line.

TABLE 5
SINGLE-DEGREE ANALYSIS OF TREATMENTS

Material	Standard			Modification			Net sum	Divisor	S.S.
Conc., parts per 10,000	250	25	2½	250	25	2½			
Total of reactions mm.	29.24	15.08	5.57	33.77	19.03	7.05			
Between materials	−1	−1	−1	+1	+1	+1	+ 9.96	30	3.31**
Linear regression	+1	0	−1	+1	0	−1	+50.39	20	126.96**
Non-parallelism	+1	0	−1	−1	0	+1	− 3.05	20	0.47
Curvature	+1	−2	+1	+1	−2	+1	+ 7.41	60	0.92
Opposed curvature	+1	−2	+1	−1	+2	−1	+ 1.89	60	0.06

**Highly significant

Each sum of squares (or each mean square) in Table 5 may be referred to the general error in Table 4 (0.27). The low mean squares in the last three rows show that the regressions were essentially linear and closely parallel. This is also apparent from the plotted points in Figure 2. The occurrence of parallelism as well as linearity has been the usual experience in the present studies, where qualitatively and quantitatively similar allergen preparations have been compared. Usually *a priori* knowledge allowed the selection of concentrations such that the average response from preparation to preparation did not vary greatly, and such that the responses obtained were in the range of linearity and of the greatest sensitivity to a change of concentration. With preparations which were qualitatively dissimilar or differed widely in potency, a lack of parallelism was sometimes noted. In such cases relative potency can be stated for specific levels only.

In the present example the log of the ratio of potency can be derived from the formula of Bliss and Marks, $(KID)/B$; where D and B are the square roots of the "Material" and "Regression" sums of squares, respectively; K is a constant depending on the number of concentrations employed (here 1.633); and I is the interval of log-concentration (here 1). The log-difference is thus $(1.633)(1)((3.31^{1/2})/126.96^{1/2}$, or 0.264. The modification is, therefore, estimated as being 1.84 times as potent as the standard.

The standard error of the log-ratio can be estimated here as (s/b). $(2/n')^{1/2}$; where s is the standard deviation of an individual cow-treatment mean $(0.27^{1/2})$; b is the common regression coefficient of reaction on concentration (estimated as net-sum/divisor for regression, or 50.39/20); and n' is the total number of cow-treatment means for one preparation (here 15). This gives an estimate of 0.075. In general

where 5 cows, with 10 to 15 replications per cow, have been used, and where the variation in materials has been similar to that in the present example, standard errors have been 0.10 or less. Thus, a log difference of 0.20 or more (corresponding to potency ratios greater than 1.59 or less than 0.63) would appear as significant. When 10 cows, with one replication per cow, and substances varying more widely have been used, standard errors have been 0.20 or higher.

The difference in standard errors just noted raises a question as to the relative influence on experimental error of several sources of variance. Experimental error in these studies may be considered as stemming from three sources: (1) cow by treatment interaction (between-cow) (2) region by treatment interaction, and (3) cow by region by treatment interaction plus measurement errors, etc. (within cow). In experiments of the "complete" blocks type, where the same number of replications appear in a given region on all cows, source 2 may be considered as a non-random variable, and therefore not a source of error. This requires, of course, that regions be well enough defined so that they are adhered to closely on all cows. The relative importance of variance sources 1 and 3 can be estimated from experiments like the ones for which error sizes were just cited. These estimates indicated that source 3 (within-cow) accounted for at least 70% of the total variance attributable to sources 1 and 3 combined.

In the example given, *a priori* knowledge allowed the selection of a number of concentrations (three) at the levels which placed them in the useful part of the response range. Thus, satisfactory comparisons were obtained. Under some conditions as few as two concentrations may be successfully used but with materials of unknown or widely varying potency, more concentrations are desirable.

AN INCOMPLETE BLOCKS DESIGN

In this experiment it was desired to compare 16 allergen preparations. Knowledge concerning the materials was such that it was desirable to study at least 4 concentrations of each, spaced at four-fold intervals. Thus there were 64 treatments to be compared. The field workers wished to use only 16 injection sites in each of the 4 compound response regions previously described; i.e., 64 sites per cow. In each of these regions, or blocks, 4 of the 16 preparations were injected, each at all 4 concentrations. Thus a complete replication could be placed on a single cow, and by using the "balanced lattice" plan for 16 treatments, every treatment could be brought together within a block with every other treatment an equal number of times in 5 replications. Ten cows were

used, thereby furnishing two complete duplications of the basic design.

Part of the 16 preparations were of tuberculin and part of johnin. In order to study specificity, therefore, all 16 preparations were compared on 10 tuberculin- or "bovis"-sensitized cows in one test. In a second test all preparations were compared on johnin- or "para"-sensitized cows. The results for the first test are cited here.

In evaluating the data, the log-concentration required to yield a skin thickening of 3 mm. was estimated by regression from the four concentrations of each substance in each block separately. The resulting 160 figures were then analyzed in the standard manner for a balanced lattice with two duplications. The analysis is shown in Table 6.

TABLE 6

ANALYSIS OF VARIANCE, LOGS OF CONCENTRATION REQUIRED FOR 3 MM. REACTION, BOVIS-SENSITIZED

	Degrees of freedom	Sum of squares	Mean square
Cows	9	21.25	2.36
Treatments (ignoring blocks)	15	169.23	11.28
Blocks (adjusted)	30	17.79	0.59
Error (intra-block)	105	31.20	0.30

The fact that the adjusted block mean square is almost twice the size of the intra-block error mean square indicates that this design yielded more precise comparisons than if all 64 treatments had been randomly distributed over each cow disregarding response regions. Unfortunately, however, through a misunderstanding, the blocks as outlined were not placed exactly as intended on the regions of varying sensitivity. This lowered the precision to some extent. Nevertheless, in the case of the bovis-sensitized cows, the lattice design showed a gain of 8% over the corresponding randomized complete blocks design. In the case of the para-sensitized cows little gain was observed.

In a later trial with 16 strong and similar allergens, and better definition of regions, a more clear-cut gain was reported, reaching over 50%. The experience gained in the whole series of studies conducted indicates that incomplete block designs of the type cited are promising where large numbers of similar treatments are to be compared.

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THE GENERAL THEORY OF PRIME-POWER LATTICE DESIGNS*

II. DESIGNS FOR p^n VARIETIES IN BLOCKS OF p^s PLOTS, AND IN SQUARES

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INTRODUCTION

An earlier paper [4] contained the basis of the design and analysis of lattice (or quasi-factorial) designs for a number of varieties (p^n) which is the power of a prime number (p), with a discussion of arrangements in p^{n-1} blocks of p plots. The procedure consisted entirely of relating the p^n varieties to the combinations of n factors, each having p levels, and utilizing the concepts of effects and interactions of these factors [3] in both the design and analysis.

The purpose of the present paper is to give designs for p^n varieties in blocks of p^s plots, where s is an integer greater than unity, and designs which utilize the Latin Square and split-plot principles. There will be little need to discuss the analysis of these designs, as this follows directly from the general formulation given in the earlier paper. It is intended however to present later more detailed numerical descriptions of the analyses of designs which appear to be of considerable practical value.

DESIGNS FOR p^n VARIETIES IN BLOCKS OF p^s PLOTS

The use of blocks of size p for p^n varieties necessitates at least n replicates, if intra-block information on all effects and interactions for the corresponding factorial scheme is to be obtained. In the case of 512 varieties for example, correspondence with the 2^9 factorial system is established and with blocks of 2 plots at least nine replicates are required. In many cases it is impossible for the experimenter to use n or more replicates, and it is then necessary to use blocks of size p^2 or p^3. If at least n replicates are to be used, there seems little point in using a design with blocks of p^2 rather than blocks of p plots. It is intended to present here some considerations on this aspect of the problem.

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For purposes of illustration designs for $3^4(=81)$ varieties will be considered first. With blocks of 3 plots, at least 4 replicates must be used, but with blocks of 9 plots the minimum number of replicates is two. With blocks of 9 plots 8 degrees of freedom must be confounded in each replicate and, denoting the pseudo-factors by a, b, c, d, the best scheme of confounding for two replicates is to confound A, B, AB, AB^2 in one replicate and C, D, CD, CD^2 in the other. This is equivalent to regarding the experiment as a 9^2 experiment with two pseudo-factors X, Y each with 9 levels, and confounding X in one replicate and Y in the second. From the general formula given earlier, the mean variance of varietal comparisons in this case will be

$$\frac{2}{40}\left\{\frac{8}{w+w'}+\frac{32}{2w}\right\}=\frac{2}{5}\left\{\frac{1}{w+w'}+\frac{4}{2w}\right\}.$$

If three replicates are to be used, the confounding in each replicate may be chosen so that no contrast is confounded in more than one replicate; for example by using the above two replicates and a third in which ABC, AB^2D, AC^2D^2 and BC^2D are confounded, and in this case the mean variance of varietal comparisons will be

$$\frac{2}{40}\left\{\frac{12}{2w+w'}+\frac{28}{3w}\right\}=\frac{1}{5}\left\{\frac{3}{2w+w'}+\frac{7}{3w}\right\}.$$

Both of the above results are given by Cox, Eckhardt and Cochran [2] with a detailed description of the analyses of the two experiments. These examples do not illustrate all the principles involved because they may be described as simple and triple lattices respectively for k^2 varieties in blocks of k plots, k being 3^2.

To illustrate the problem in full generality the case of $2^5(=32)$ varieties in blocks of $2^2(=4)$ plots will be described. The corresponding factorial scheme consists of five factors which will be denoted by a, b, c, d, e, each having two levels. In order to reduce the size of block to 4 plots, it will be necessary to confound seven degrees of freedom in each replicate. The following is a suitable scheme for three replicates:

replicate 1 confounding A, B, AB, C, AC, BC, ABC;

" 2 " A, C, AC, D, AD, CD, ACD;

" 3 " B, D, BD, E, BE, DE, BDE;

The analysis of variance for this experiment will be as follows:

TABLE 1
ANALYSIS FOR 2^5 VARIETIES IN BLOCKS OF 4 PLOTS

	DF	Expectation of Mean Square
Replicates	2	
Blocks adjusted for varieties		
Comparison of effects and interactions between the two replicates in which they are confounded.	5	$\sigma_i^2 + 4\sigma_b^2$
Comparison of effect or interactions in the two replicates in which they are confounded with corresponding effect or interactions in replicate in which they are unconfounded	5	$\sigma_i^2 + 1/3 \cdot 4\sigma_b^2$
Comparison of effect or interaction confounded in one replicate with mean unconfounded effect in the other two replicates	11	$\sigma_i^2 + 2/3 \cdot 4\sigma_b^2$
Varieties ignoring blocks	31	
Intrablock error	41	σ_i^2
Total	95	

The effects and interactions A, B, C, AC, and D on a per-plot basis will be determined with variance $1/8(w + 2w')$, effects and interactions E, AB, BC, ABC, CD, ACD, BD, BE, DE, and BDE with variance $1/8(2w + w')$ and the remaining interactions with variance $1/8(3w)$, where $w = 1/\sigma_i^2$ and $w' = 1/(\sigma_i^2 + 4\sigma_b^2)$. The mean variance of varietal comparisons will be, by formula of the earlier paper [4],

$$\frac{2}{31}\left\{\frac{5}{w + 2w'} + \frac{10}{2w + w'} + \frac{16}{3w}\right\}.$$

The total number of different schemes for a p^n system in blocks of p^s plots is equal to

$$\frac{(p^n - 1)(p^n - p)(p^n - p^2) \cdots (p^n - p^{n-s-1})}{(p^{n-s} - 1)(p^{n-s} - p)(p^{n-s} - p^2) \cdots (p^{n-s} - p^{n-s-1})}$$

and the practical problem is to choose out of all these schemes, a number of schemes, one for each replicate, in such a way that the confounding is distributed as equally as possible over all the effects and interactions. Suitable schemes for p^{2n} varieties in blocks of p^n plots are directly obtainable from completely orthogonalised squares of side p^n, which are published in the literature or may be generated by the method described by Stevens [6]. Suitable schemes for three replicates of p^{3n} varieties in

blocks of p^n plots are obtainable as described by Yates [7] for the three-dimensional lattice. The following schemes for other cases seem worthy of mention (there is little point, for example, in giving a design for 2^7 $(=128)$ varieties in blocks of 4 or 8 plots, since designs for $5^3(=125)$ varieties in blocks of 5 plots are likely to be quite satisfactory), generators only of the schemes of confounding being given:

32 varieties in blocks of 8 plots:

replicate 1, $A, B,$
" 2, $C, D,$
" 3, $AC, DE,$

the efficiency factor being 87 percent.

256 varieties in blocks of 8 plots:

replicate 1, $A, B, C, D, E,$
" 2, $D, E, F, G, H,$
" 3, $A, B, C, F, G,$

the efficiency factor being 81 percent.

243 varieties in blocks of 9 plots:

replicate 1, $A, B, C,$
" 2, $A, B, D,$
" 3, $C, D, E,$

the efficiency factor being 90 percent.

There is also available a wide range of designs for p^n variates using the split-plot analogy. Thus with 4 pseudo-factors a, b, c and d, it is possible to confound A with blocks of p^3 plots, B with blocks of p^2 within blocks of p^3, C with blocks of p within blocks of p^2, D being unconfounded. In this case, four replicates give a design with reasonable balance. These designs will not be discussed in detail here, because the split-plot principle is used to the best advantage when whole plots are subject to two restrictions. An example of this type is given later.

THE COMPARISON OF LATTICE DESIGNS WITH DIFFERENT SIZES OF BLOCK

Cox, Eckhardt and Cochran [2] gave the analysis for 9^2 varieties in blocks of 9 using three replicates such as those given above, and these replicates were duplicated. The approach of the present papers suggests a different design for this particular case, since the 81 varieties may be regarded as making up a 3^4 system and blocks of 3 plots may be used. It would be possible to use the following confounding

replicate 1:	$A, B, C,$	and all their interactions
	2: $A, B, D,$	" " " "
	3: $A, C, D,$	" " " "
	4: $B, C, D,$	" " " "
	5: $AB, AC, AD,$	" " " "
	6: $AB^2, AC^2, AD^2,$	" " " "

The mean variance of comparisons with this design is

$$\frac{1}{20}\left\{\frac{3}{2w+4w'}+\frac{11}{3w+3w'}+\frac{9}{4w+2w'}+\frac{15}{5w+w'}+\frac{2}{6w}\right\}.$$

For various values of w/w', the efficiency of each of these designs relative to complete randomised blocks is as follows:

	w/w'									
	1	2	3	4	5	6	7	8	9	10
3 replicates of 9^2	100	104	111	118	126	134	143	151	160	168
6 replicates of 3^4	100	110	126	144	163	183	202	222	242	262

The ratio w/w' will not be the same for both designs laid out on the same land, since in the upper case the relevant variances are those within blocks of 3 and between blocks of 3 amongst 81 plots, while in the second case the relevant variances are those within and between blocks of 9 plots.

The empirical law of soil heterogeneity obtained by Fairfield Smith [5] may be used to obtain a partial answer to this question. He postulated the relationship

$$V_x = V_1/x^b,$$

where V_x is the variance per unit area with plots of size x, V_1 is the variance per unit area with plots of unit area, and b is a parameter depend-

ing on the extent of heterogeneity in the experimental area. He further obtained the relationship

$$\frac{(V_x)n}{(V_x)m} = \frac{(m-1)(n-n^{1-b})}{(n-1)(m-m^{1-b})},$$

to give the expectation of the relative efficiency of a randomised block experiment with m plots relative to one with n plots per block, $(V_x)_m$ being the variance of a mean per unit area with m plots of size x units per block, and $(V_x)_n$ being defined similarly.

With these relationships the relative values of the ratios w/w' for blocks of 3 and blocks of 9 within a replicate of 81 plots may be obtained. Consider the analysis given in Table 2.

TABLE 2

ANALYSES OF VARIANCE FOR BLOCKS OF THREE AND BLOCKS OF NINE WITHIN A BLOCK OF 81 PLOTS

	Degrees of freedom	Mean square	Sum of squares
Total	80	α	80α
Blocks of 3			
Among blocks	26	δ	$26\delta = 80\alpha - 54\beta$
Within blocks	54	β	54β
Blocks of 9			
Among blocks	8	ϵ	$8\epsilon = 80\alpha - 72\gamma$
Within blocks	72	γ	72γ
Among blocks of 3 within blocks of 9	18	λ	$18\lambda = 72\lambda - 54\beta$

Now, the sums of squares 80α and 72γ may be computed from the following relations—respectively,

$$\frac{\alpha}{\delta} = \frac{(V_x)_{81}}{(V_x)_3} = \frac{2}{80}\left\{\frac{81-81^{1-b}}{3-3^{1-b}}\right\} = \frac{54}{80}\{1+3^{-b}+3^{-2b}+3^{-3b}\},$$

$$\frac{\gamma}{\delta} = \frac{(V_x)_9}{(V_x)_3} = \frac{2}{8}\left\{\frac{9-9^{1-b}}{3-3^{1-b}}\right\} = \frac{6}{8}\{1+3^{-b}\},$$

β may be taken equal to unity, and the quantities α, γ, δ, and ϵ may be evaluated in terms of b. For various values of b the ratio w/w' may be computed for blocks of 3 and blocks of 9 within a replicate of 81 plots.

It was found that $w/w'(=\epsilon/\gamma)$ for blocks of 9 plots was approximately 1.55 times $w/w'(=\delta/\beta)$ for blocks of 3 plots within a replicate of 81 plots.

The quantity b ranges from zero to unity, unless these are negative correlations between plots in a block (or competition) when it can exceed unity by a small amount depending upon the size of the block. The maximum value that w/w' can take for blocks of 3 is (for $0 \leq b \leq 1$) 81/13, and for blocks of 9 it is 9. In practice, however, there appears to be no limit to the value for w/w' for any design. More information is needed then to obtain a complete answer for the relative values of w/w' for the two designs, incomplete blocks of 3 and of 9. Fairfield Smith was unable to verify his law for small values of b, and it appears that the relationships postulated by him are not very accurate for values of b less than 0.2. Extensive uniformity trial data would need to be examined before a relationship could be postulated for small values of b. The above suggests however that for most types of soil heterogeneity the design with blocks of 3 plots will yield more information than that with blocks of 9 plots.

DESIGNS WITH TWO RESTRICTIONS

Lattice designs for a number of varieties k^2, with two restrictions have been described by Yates [8] who has called them lattice squares, and by Cochran [1]. Such designs are based on completely orthogonalised Latin Squares of side k, and since such squares exist when k is a prime number or a power of a prime, the present treatment may be extended to this case. If for example the number of varieties is 25, the effects and interactions may be represented by A, B, AB, AB^2, AB^3 and AB^4, each with 4 degrees of freedom, and it is possible to form squares such that each effect or interaction is confounded, with the rows or with the columns of one square. For the semi-balanced design A is confounded with rows and B with columns in one square, AB with rows and AB^2 with columns in a second square, and AB^3 with rows and AB^4 with columns in a third square. The information on effects A, AB, and AB^3 will be $5^2(2w + w_r)$, and on effects A, AB^2, AB^4, it will be $5^2(2w + w_c)$, where w is the reciprocal of the intra-row and intra-column variance, and w_r and w_c are respectively the reciprocals of the inter-row and inter-column variances. If the intra-row and intra-column variance is σ_i^2 and the additional variance between rows is σ_r^2 and between columns σ_c^2, w will be equal to $1/\sigma_i^2$, w_r to $1/(\sigma_i^2 + p\sigma_r^2)$ and w_c to $1/(\sigma_i^2 + p\sigma_c^2)$. The mean variance of varietal comparisons will be, by analogy with results in the earlier paper,

$$\frac{2}{6}\left\{\frac{3}{2w + w_r} + \frac{3}{2w + w_c}\right\} = \left\{\frac{1}{2w + w_r} + \frac{1}{2w + w_c}\right\}.$$

It is clear furthermore that the use of two squares only is a valid design: if for example the first two of the above are chosen, the mean variance of varietal comparisons will be

$$\frac{2}{6}\left\{\frac{2}{w + w_r} + \frac{2}{w + w_c} + \frac{2}{2w}\right\}$$

$$= \frac{2}{3}\left\{\frac{1}{w + w_r} + \frac{1}{w + w_c} + \frac{1}{2w}\right\}.$$

If $6(=p + 1)$ squares are used, each effect may be confounded with rows and with columns, and the mean variance per comparison is

$$\frac{2}{6}\left\{\frac{6}{4w + w_r + w_c}\right\} = \frac{2}{4w + w_r + w_c}.$$

The analysis of the completely balanced lattice square has been given by Yates [8] but it seems worth while to describe it briefly in terms of the concepts used in the present paper. Taking for example the case when $p = 5$, there will be 6 squares in all, the confounding being for example:

	Confounded with	
Square	Rows	Columns
1	A	B
2	AB	AB^2
3	AB^3	AB^4
4	B	A
5	AB^2	AB
6	AB^4	AB^3

It may be noted that with a particular factorial correspondence more than one system of confounding is possible. Estimates of the A effect are obtained from square 1 with a variance based on $(\sigma_i^2 + 5\sigma_r^2)$, square 4 with a variance based on $(\sigma_i^2 + 5\sigma_c^2)$ and from each of the remaining squares with a variance based on σ_i^2; and these estimates are combined weighting inversely as their variances. The estimation of $(\sigma_i^2 + 5\sigma_r^2)$ is performed by noting the comparison of the A effect in square 1 with the average A effect in squares 2, 3, 5 and 6 will contain only intra-row and intra-column and row errors. In fact, the contribution of square 1 to

the sum of squares for rows, eliminating varieties and columns is

$$\frac{1}{100}\left\{\sum_i (4(A)_{i1} - \overline{(A)_{i2} + (A)_{i3} + (A)_{i5} + (A)_{i6}})^2 - \frac{(4 \times \text{total of square 1} - \text{sum of totals of squares 2, 3, 5, 6})^2}{5}\right\}$$

where $(A)_{ij}$ is the total of plots at level i, in square j. The contribution of square 1 to the sum of squares for columns eliminating treatments is

$$\frac{1}{150}\left\{\sum_i (5(B)_{i1} - \overline{(B)_{i2} + (B)_{i3} + (B)_{i4} + (B)_{i5} + (B)_{i6}})^2 - \frac{(5 \times \text{total of square 1} - \text{sum of totals of squares 2, 3, 4, 5, 6})^2}{5}\right\}.$$

The identity of these expressions with those given by Yates is not immediately obvious and his method is the more expeditious computationally. The identity of the adjusted variety means by the present treatment with those given by Yates is easily verified. Corresponding formulas for designs in which only a selection of the total $(p + 1)$ squares are used may be written down at sight of the structure of the design.

The restriction of the term lattice squares to arrangements of k^2 varieties in squares of side k, when a completely orthogonalised Latin Square of side k exists appears unduly restrictive. In the case of number of varieties k^2 where k is quite general except that a Latin Square of side k exists, it is possible to utilize the effectiveness of the Latin Square arrangement in controlling heterogeneity. The k by k Latin Square gives three orthogonal groupings of the k^2 varieties in k groups of k, by rows, columns and letter. If these groupings are denoted by α, β, and γ respectively it is entirely feasible to use three k by k squares or a multiple of these with the following confounding:

	Square I	Square II	Square III
Confounded with			
Rows	α	β	γ
Columns	β	γ	α

The advantages of lattice square arrangements relative to lattice arrangements depend to some extent on the shape of plot to be used (1). In corn yield tests it is customary to use plots of size 2 by 10 hills and for this shape of plot lattice square arrangements are not likely to yield

much greater precision than lattice arrangements, in addition to the fact that they result in awkward shaped replicates. If however it is possible to use plots which are more nearly square the lattice square arrangement will almost certainly be more advantageous. Under such circumstances the design given above would appear to be appropriate. This design may be called an unbalanced lattice square, the situation being analogous to the case of lattice designs with one restriction, in that simple and triple lattices are always possible for k^2 varieties but that the balanced lattice exists only if a completely orthogonalised Latin Square of side k exists.

UTILIZING THE LATIN SQUARE AND SPLIT-PLOT PRINCIPLES

A detailed enumeration of all possible designs will not be given, but the following are simple extensions.

If p^3 varieties are being tested, they may be represented formally as the combinations of three factors a, b, c and factors a and b may be imposed as whole-plot treatments and c as a split-plot treatment. The whole-plot factors may be estimated by the use of lattice squares with at least two replicates, each plot of the squares being split for the factor c. In these cases information will be of four types

(a) inter-row with variance $1/w_r$,
(b) inter-column with variance $1/w_c$,
(c) intra-row and column with variance $1/w$,
(d) intra-whole plots with variance $1/w_s$,

If for example each of the factors has 5 levels, a suitable set of three replicates is given by

	Confounded with Rows	Confounded with Columns	Lattice Square plots split for
Square 1	A	B	C
2	AB	AB^2	C
3	AB^3	AB^4	C

For the estimation of the effects A, B and interactions AB, AB^2, AB^3, AB^4, the procedure is the same as if the plots of the square were not split. An estimate of the split-plot error σ_s^2 $(=1/w_s)$ may be obtained from the interaction with squares of all two and three factor interactions involving c. The mean variance of varietal comparisons will be

$$\frac{2}{31}\left\{\frac{3}{2w + w_r} + \frac{3}{2w + w_c} + \frac{25}{3w_s}\right\}.$$

It is possible to use a design similar to the above with only two replicates when the number of varieties is p^2q where q is not equal to p and need not be a prime. In such a case, however, while the analysis will be of a similar structure, the mean variance of varietal comparisons is not quite as obvious, and as the purpose of the present paper is to deal with prime-power lattice designs, it will not be discussed here.

It is quite probable that with such a layout w_r and w_c will be very small and w will be small in comparison with w_s. In order to improve the accuracy of the experiment, the following scheme may be followed.

	Confounded with		Lattice Square
Replicate	Rows	Columns	plots split for
I	A	B	C
II	C	A	B
III	B	C	A

With such a design the variance of the A, B, and C effects will be $1/p^2(w_r + w_c + w_s)$, the variance of the interactions AB, AB^2, AB^3, AB^4, AC, AC^2, AC^3, AC^4, BC, BC^2, BC^3, and BC^4 will be $1/p^2(w + 2w_s)$, and for all interactions involving three factors the variance will be $1/p^2(3w_s)$. The mean variance of varietal comparisons will be

$$\frac{2}{31}\left\{\frac{3}{w_r + w_c + w_s} + \frac{12}{w + 2w_s} + \frac{16}{3w_s}\right\}.$$

The analysis will follow the general lines of the present and previous paper [4]. The weights for row comparisons, column comparison, whole plot and split-plot comparisons may be obtained from:

The mean square for rows eliminating varieties and columns and whole plots, which is obtained from the comparison of main effects in squares in which they are confounded with rows with the same main effects in squares in which they are unconfounded with rows, columns or whole-plots:

The mean square for columns, eliminating varieties and rows and whole plots obtained likewise:

The error mean square for whole plots, obtained from the comparison of two-factor interactions in the squares in which they are confounded with whole-plots with the same interacactions in the other two squares in which they are unconfounded;

The split-plot error mean square, obtained from the comparison

of two-factor interactions amongst squares in which they are unconfounded, and the interaction of the three-factor interactions with the three squares.

This design appears to be eminently suited for corn breeding work in which the basic plot is long and narrow. It is customary to use plots of size 2 by 10 hills and the arrangement of p of these (for small p) in a whole-plot would result in whole plots that are more or less square and the full advantages of the Latin Square control of row and column effects would be utilizable.

Alternatively to the above split-plot design for p^3 varieties, we may, as Yates [9] pointed out, divide the varieties into p groups of p^2 varieties and test each group of p^2 varieties with $p \times p$ lattice squares, of which only two are absolutely necessary for each group. The division into p groups of p^2 varieties may be made by choosing one effect or interaction to be confounded with groups in each replicate, and a large number of possible groupings are available. If the pseudo-factors are denoted by a, b, c, the possible replicates are obtained by choosing one effect or interaction to be confounded with squares and other interactions to be confounded with rows and columns within squares: if the factors each have 5 levels, for example, the following are 9 suitable replicates:

	Confounded with	
Squares	Rows	Columns
A	B	C
A	BC	BC^2
A	BC^3	BC^4
B	C	A
B	AC	AC^2
B	AC^3	AC^4
C	A	B
C	AB	AB^2
C	AB^3	AB^4

This table could be extended (a) by interchanging rows and columns and (b) by confounding between squares each of the possible 31 effects and interactions. The minimum number of replicates which must be used is four, whatever the value of p, but such a design would have a low relative efficiency. Information in such a design consists of:

(a) among squares,
(b) among rows within squares,
(c) among columns within squares,
(d) within row and columns,

and the relative efficiency may be evaluated in terms of the variances of these types of information. As stated by Yates [9] the efficiency factor of the design given above (the ratio of the mean variance of varietal comparisons in complete randomised blocks to the mean variance in the design when information other than within rows and columns is assumed to be valueless and when the error variance is assumed to be the same in both designs) is

$$\frac{(p-1)(p^2+p+1)}{(p+1)(p^2+p+2\frac{1}{2})}.$$

This factor is obtained by noting that the three main effects will be determined with variance $1/(p-1)w$ and the remaining (p^2+p-2) effects and interactions with variance $2/3(p-1)w$ so that the mean variance of varietal comparisons would be

$$\frac{2(p-1)}{(p^{3-1})}\left\{\frac{3}{(p-1)w}+\frac{2(p^2+p-2)}{3(p-1)w}\right\}=\frac{4}{3w}\left\{\frac{(p^2+p+2\frac{1}{2})}{(p^2+p+1)(p-1)}\right\}.$$

compared with $4/3(p+1)w$ with complete randomised blocks and the same error variance.

A further extension is the testing of p^4 varieties involving pseudo factors a, b, c and d in which factors a and b are applied in a lattice square arrangement, the plots being split for factors c and d which are also applied in a lattice square arrangement.

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ASSAYS OF INSULIN WITH ONE BLOOD SAMPLE PER RABBIT PER TEST DAY

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Biological determinations of potency are subject to a sampling error internal to each assay and also to variation between independent assays. The first component, sometimes designated as s_M , is readily computed from the data of a single self-contained assay. To evaluate the second component requires two or more independent experiments. It is usually assumed to be negligible and the reliability of an assay is estimated from its internal variability. The validity of this assumption can be checked only by reassaying a single unknown independently on two or more occasions. As results are reported with a given technique the confidence to be placed upon its internal error can be assessed.

During 1944 an investigation [1] was made of the efficiency of a number of procedures for use in the rabbit assay of insulin. The most promising of these required only one sample of blood for glucose analysis from each rabbit on each test day. During a year's experience with this single-blood-sugar method twenty-one insulin samples of unknown potency were assayed against the standard and seven samples of unknown potency with other samples of unknown potency. The samples had been prepared from a variety of sources (beef, pork and lamb) and varied in purity. Since the number of assays conducted on any one sample ranged from two to eight, it has been possible to compare the two sources of error.

METHOD

The rabbits used in the assays were of mixed stock; they were free from disease so far as could be determined by a superficial examination; and, except for the occasional animal, they ranged in weight from 1.6 to

3.0 kg. The rabbits were fed Purina Rabbit Chow (Complete Ration) and water was available to them at all times. Before the rabbits were injected with insulin, they were starved for a 16 to 18 hour period. The specified quantities of insulin were then injected in 2 ml. of U.S.P. XII [2] diluting fluid, using the marginal ear veins as the route of injection. Fifty minutes after injection of insulin, slightly more than one ml. of blood was taken from a marginal ear vein. Blood glucose in mgm. per-cent was determined by the method of Nelson [3] and the values obtained were used directly in computing the results. Rabbits placed on test on successive days were starved for the length of time specified, injected with insulin, bled as described, and then given access to food for 4 to 5 hours before being starved for the next day's treatment.

Between February, 1945, and March, 1946, 102 twelve-rabbit assays of insulin were carried out using the technique described. Assays were conducted each month during this period. The design, employing three separately randomized latin squares, was patterned after that outlined by Bliss and Marks [4]. Each rabbit received one dose of insulin on each of four successive working days. Except when one unknown preparation of insulin was being assayed against a second unknown, dose S_1 contained 0.60 units and dose S_2 1.2 units of Insulin Standard.[1] On the basis of an assumed potency for the unknown under assay, doses U_1 and U_2 were made up to contain 0.60 and 1.2 units of insulin respectively. The order of injection and the resulting blood-sugar determinations in one assay (No. 22) are exemplified in Tables 1 and 2. Table 3 illustrates the calculation from these data of the potency and its error in a self-contained assay.

[1]Insulin Standard S230, 23.0 International Units per mgm. (kindly supplied by the Insulin Committee, University of Toronto).

TABLE 1
ORDER OF INJECTIONS
ASSAY NO. 22

Rabbit Number	1	2	3	4	5	6	7	8	9	10	11	12
Date												
23/4/45	S_2	U_1	U_2	S_1	S_2	U_1	U_2	S_1	U_1	U_2	S_1	S_2
25/4/45	S_1	U_2	U_1	S_2	U_2	S_1	S_2	U_1	U_2	U_1	S_2	S_1
26/4/45	U_1	S_1	S_2	U_2	S_1	U_2	U_1	S_2	S_2	S_1	U_1	U_2
27/4/45	U_2	S_2	S_1	U_1	U_1	S_2	S_1	U_2	S_1	S_2	U_2	U_1

TABLE 2

RESPONSE—EXPRESSED AS MG. PERCENT OF BLOOD SUGAR

ASSAY NO. 22

Rabbit Number	1	2	3	4	5	6	7	8	9	10	11	12	
Date													Total
23/4/45	27	54	48	63	24	50	34	48	61	72	68	28	577
25/4/45	36	40	72	50	33	58	56	60	58	83	62	65	673
26/4/45	54	61	60	50	57	26	59	46	46	75	68	54	656
27/4/45	38	36	60	59	46	35	61	47	54	62	50	56	604
Total	155	191	240	222	169	169	210	201	219	292	248	203	2,510

Total for Doses

Dose	S_1	S_2	U_1	U_2
Response	706	532	722	550

The rabbits employed for the work did not appear to suffer from the frequent injections of insulin and, if allowed a week's rest between assays, rabbits could be used 4 or 5 times. Convulsions were extremely rare. Out of the 4896 blood-sugar determinations which would have been required for a complete record only 29, or approximately 0.6%, were lost

TABLE 3

CALCULATION OF ESTIMATE OF POTENCY AND ITS STANDARD ERROR

ASSAY NO. 22

Treatment Effect	Factorial Coefficient (x) for log. dose				N* $\Sigma(x^2)$	$\Sigma(xY_p)$	Mean Square $\Sigma^2(xY_p)$
	S_1	S_2	U_1	U_2			$N\ \Sigma(x^2)$
Samples	−1	−1	+1	+1	48	34	$24.08 = D^2$
Slope	−1	+1	−1	+1	48	−346	$2494.08 = B^2$
Parallelism	+1	−1	−1	+1	48	2	0.83
Totals for Doses = Y_p	706	532	722	550	Error Variance (s^2) = 45.72		

*N (the number of responses at each dose level) = 12

M (the log. of the potency ratio U/S) = ID/B = −0.0296

s_M (the standard error of M) = $(sI(B^2 + D^2)^{1/2})/B^2$ = 0.0409

where I (the log. of the potency ratio S_2/S_1 and U_2/U_1) = 0.301

for all reasons. These lost results were replaced, for computational convenience, by means of a formula suggested by DeLury (12).[2]

RESULTS

The results of the 102 assays were used to compute the estimate in Table 4 of the standard deviation (s), the slope (b), and the relative potency based upon the assay slope. The date on which the assay was begun, the degrees of freedom for error and the factorial difference between the responses on standard and on unknown are also given in this table. Save in five instances, there was no significant departure from parallel dosage-response curves for standard and unknown insulin. This is about the number of departures to be expected in such a series.

The agreement of the error variances with their mean of $s^2 = 53.13$ was tested with Bartlett's equation for χ^2 [5]. The resulting χ^2 (258.4; $n = 101$) indicated a highly significant heterogeneity among the variances obtained from the different assays. The standard deviation (s) of an individual blood-sugar determination computed from the average variance was 7.29.

The standard deviation (s) for each individual assay has been plotted against the date it was started (Control Chart). The value based on the average variance has been plotted as a solid horizontal line and the limits expected to enclose 95% of the observations as parallel broken lines. No adjustment has been made in the limits for the occasional assay with fewer than 30 degrees of freedom. Of the 102 assays considered, 23 had standard deviations which fell outside of the control limits. Visual inspection of the control chart might suggest that the standard deviation tended to increase in magnitude from February to October of 1945. Such a trend could be due to seasonal variation in the experimental animals or to some unknown factor having to do with the experimental technique.

The mean square for the interaction of Slope X Assay was 57.87 with 101 degrees of freedom, which is not significantly different, by the usual "F" tests, from the average error variance. This would suggest that the slope for the logarithm-dosage response curve remained stable over the

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[2] If the estimate of the value to be replaced be designated as Y, then

$$Y = \frac{4T_1 + 4T_t + 4rT_e - 2T}{12r - 6}$$

where T_1, T_t and T_e are the respective totals for the row, treatment, and column in which the observation is missing; T is the total for all responses in the experiment from which the observation is missing; and r is the number of 4×4 latin squares used in the experiment.

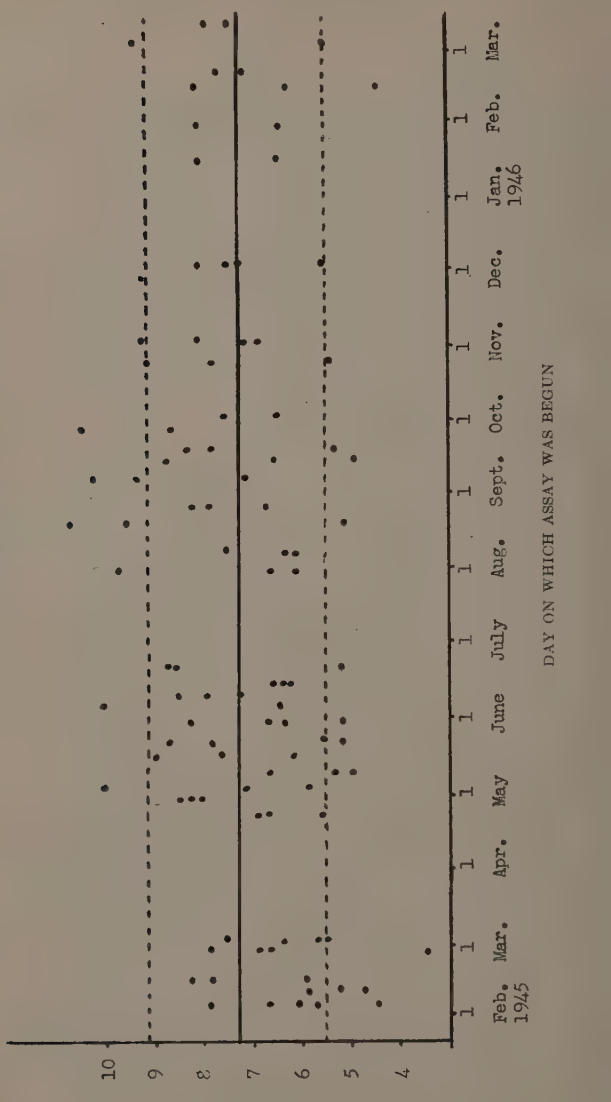

FIGURE 1
CONTROL CHART

period. The average slope of -41.44 was used in recomputing the potency of each assay. No correlation was found between the values of s and of b computed separately from the 102 assays.

The variation in independent estimates of potency of the same preparation was assessed from the factorial differences in Table 4. The mean square between replicates was 46.18 with 74 degrees of freedom. Since this was less than the average error variance within assays, there was no evidence of a variance component between assays in addition to that observed within assays.

The expected precision of an assay ($s_M = s/b\ (1/12)^{1/2}$) [see ref. 6], using the average variance and slope, was found to be 0.0508. The corresponding quantity computed from the variation among results of replicated assays was 0.0488 when the individual slopes were used to compute the estimates of potency, and 0.0473 when these estimates were computed with the average slope. The standard error of the estimate of potency was therefore of the order of 12%. Since the estimates of error from the two sources were in good agreement, the internal evidence of the assays provided a satisfactory basis for estimating the variability to be expected in the results of replicated tests. An average slope might be used to advantage in computing estimates of potency and its precision. In view of the lack of homogeneity among the variances, one might prefer to use the individual estimates of error.

DISCUSSION

Previous workers, employing somewhat more complicated bleeding techniques, have used adequate statistical methods to estimate the expected error of their insulin assays. Bliss and Marks [6], using eight pure-bred Himalayan rabbits and bleeding each rabbit six times on each test day, estimated the standard deviation of an estimate of potency from a twelve-rabbit assay at 7.9%. Smith, Marks, Fieller and Broom [7], using six bleedings per rabbit per test day and an alternative experimental design, obtained results with an estimated standard deviation of about 12.5% for a twelve-rabbit assay.

From the results of the 1944 investigation [1] the single-blood-sugar method would be expected to yield a more precise or more reproducible result for a given amount of labour than the more conventional procedures [8,9]. In this connection, it is of interest to note a recent communication from Bliss and Bartels [10]. After working over the data obtained by Bliss and Marks [4], these workers have concluded that the number of blood samples taken per rabbit per test day might be reduced

TABLE 4
RESULTS FROM 102 TWELVE-RABBIT ASSAYS

Assay Number	Assay Date	Insulin Sample Number	d.f. (error)	s	$-b$	Factorial Difference ($\Sigma\, xV_p$)	Estimate of Relative Potency
1	6/2/45	740	30	7.88	48.59**	67	0.88
2	"	"	30	6.75	35.71	10	0.97
3	"	"	30	5.72	44.16	9	0.98
4	"	"	30	6.10	49.14	11	0.98
5	"	"	30	4.49	47.76	−33	1.07
6	12/2/45	"	30	5.94	48.03	−19	1.04
7	"	"	30	5.28	44.16	29	0.94
8	"	"	30	4.77	34.05	−16	1.05
9	16/2/45	1990	30	7.88	41.11	117	0.76
10	"	"	30	8.22	47.34	−12	1.02
11	"	"	30	5.93	46.51	112	0.79
12	28/2/45	744	30	3.52	34.47**	−1	1.00
13	"	"	30	6.63	39.04	36	0.91
14	"	"	30	6.82	47.62	60	0.89
15	"	"	30	7.92	43.60	−25	1.06
16	5/3/45	"	30	5.45	41.12	15	0.97
17	"	"	29	5.60	45.96	26	0.95
18	"	"	30	7.57	50.39	62	0.89
19	"	"	30	6.39	45.82	−19	1.04
20	23/4/45	2056*	30	6.72	45.54	−9	1.02
21	"	"	30	5.57	32.81	−17	1.05
22	"	"	30	6.76	47.90	34	0.93
23	30/4/45	2062*	30	8.12	51.36	−21	1.04
24	"	"	30	8.46	40.14	−80	1.21
25	"	"	30	8.14	44.85	12	0.97
26	4/5/45	2073*	30	5.87	43.74	42	0.91
27	"	"	30	10.01	36.96	105	0.76
28	"	"	30	7.15	28.24	32	0.90
29	11/5/45	675–1	29	6.65	46.79	72	0.86
30	"	"	29	4.91	44.57	30	0.94
31	"	"	30	5.34	26.99**	135	0.62
32	17/5/45	2087*	30	7.62	36.54	−40	1.11
33	"	"	30	8.99	35.30	83	0.80
34	"	"	30	6.13	41.25	−44	1.11
35	23/5/45	747	29	5.46	43.74	−24	1.05
36	"	"	29	7.81	46.10	139	0.75
37	"	"	30	5.18	34.47	45	0.88
38	"	"	30	8.64	43.60	−23	1.05
39	30/5/45	"	30	6.63	31.70	5	0.98
40	"	"	30	8.23	37.65	50	0.88
41	"	"	29	6.31	28.93	27	0.91
42	"	"	28	5.16	43.74	−42	1.10
43	5/6/45	2098*	30	6.44	48.73	−1	1.00
44	"	"	30	10.00	33 78	−34	1.10

TABLE 4—*Continued*

Assay Number	Assay Date	Insulin Sample Number	d.f. (error)	s	$-b$	Factorial Difference (ΣxY_p)	Estimate of Relative Potency
45	11/6/45	2104*	30	8.51	56.34	51	0.92
46	"	"	30	7.91	42.50	−31	1.07
47	"	"	30	7.26	45.54	−7	1.01
48	15/6/45	747–00	30	6.59	41.94	−29	1.07
49	"	"	30	6.41	40.00	5	0.99
50	"	"	30	6.47	35.16	−22	1.06
51	22/6/45	714–7	30	5.20	42.08	50	0.89
52	"	"	30	8.76	46.51	−96	1.22
53	"	"	27	8.71	37.79	33	0.92
54	31/7/45	714–8	27	9.78	45.54	93	0.82
55	"	"	29	6.10	33.22	17	0.95
56	"	"	30	6.65	46.10	25	0.95
57	8/8/45	714–9	26	6.34	38.76	28	0.93
58	"	"	30	7.48	34.74	21	0.94
59	"	"	30	6.11	30.73	−16	1.05
60	20/8/45	751	30	10.71	49.00	20	0.96
61	"	"	28	5.17	40.00	−11	1.03
62	"	"	26	9.50	38.48	−50	1.13
63	27/8/45	"	30	6.67	37.10	−12	1.03
64	"	"	29	7.81	48.31	3	0.99
65	"	"	30	8.20	31.84	−36	1.11
66	7/9/45	2121	30	7.15	44.44	65	0.87
67	"	"	30	9.38	35.85	49	0.88
68	"	"	30	10.23	47.62	−20	1.04
69	14/9/45	2097A	30	6.52	54.54	−16	1.03
70	"	"	30	4.88	40.14	−2	1.00
71	"	"	30	8.77	33.49	80	0.79
72	20/9/45	496–1	30	8.32	40.97	−178	1.52
73	"	"	30	5.27	35.58	−179	1.62
74	"	"	30	7.88	38.62	−79	1.22
75	27/9/45	2150	30	8.61	38.90	−115	1.33
76	"	"	30	10.42	27.55	−49	1.19
77	3/10/45	2155	30	6.45	51.50	−66	1.13
78	"	"	30	7.57	32.67	38	0.89
79	26/10/45	2148	29	7.80	40.56	263	0.54
80	"	"	30	9.11	49.70	165	0.73
81	"	"	29	5.40	46.23**	180	0.69
82	1/11/45	755	30	8.12	44.99	−17	1.04
83	"	"	30	6.91	50.80	−55	1.11
84	"	"	30	9.25	25.88	−41	1.16
85	"	"	30	7.16	42.77	−79	1.19

TABLE 4—*Continued*

Assay Number	Assay Date	Insulin Sample Number	d.f. (error)	s	$-b$	Factorial Difference (ΣxY_p)	Estimate of Relative Potency
86	3/12/45	2201*	30	5.50	49.83	−30	1.06
87	"	"	30	7.21	53.99	−42	1.08
88	"	"	29	8.02	41.39	57	0.88
89	"	"	30	7.54	39.73	−87	1.23
90	15/1/46	758	30	8.08	55.92	−124	1.24
91	"	"	30	6.47	20.76	−24	1.12
92	29/1/46	"	30	6.40	45.26	−81	1.19
93	"	"	30	8.16	35.44	32	0.92
94	14/2/46	2141	30	6.22	34.19	−27	1.08
95	"	"	30	4.44	34.33	−64	1.20
96	"	"	30	8.06	42.77	9	0.98
97	20/2/46	2151	30	7.71	55.79	−7	1.01
98	"	"	30	7.14	39.45	43	0.90
99	4/3/46	761	30	5.49	37.65	−20	1.05
100	"	"	30	9.40	49.28	−90	1.19
101	12/3/46	"	30	7.95	34.05**	−46	1.14
102	"	"	30	7.47	42.36	6	0.99

*One sample of unknown potency assayed in terms of a second sample also of unknown potency.
**Departure from parallelism significant at 5% Leve of Probability.

without materially affecting the precision of the assay results. Lacey [11] has considered the effect of reducing the number of blood samples per rabbit per test day but has not adopted an abbreviated bleeding schedule. Pugsley and Rampton [13] have compared the results obtained when samples of insulin from different sources were assayed by the single-blood-sugar method and by a modification of the U.S.P. procedure. They found excellent agreement between results obtained by the two methods and they confirmed the conclusion that the single-blood-sugar method is the more economical procedure.

The applicability of the single-blood-sugar method of assay to insulin samples from different sources and of different degrees of purity is under study. A variety of insulin samples have been assayed both by this method and by the technique adapted from Lacey [8] by the United States Pharmacopoeia [2]. The agreement between results obtained thus far by the two methods has been encouraging. The single-blood-sugar method does not differentiate between insulins with prolonged action (such as protamine zinc insulin) and unmodified insulin.

SUMMARY

Experience gained from the performance of 102 twelve-rabbit insulin

assays has been described. In carrying out the assays, insulin was injected intravenously, and one sample of blood for glucose analysis was drawn from each rabbit on each test day 50 minutes after injection. Significant variations in the slope of the logarithm-dosage response curve were not detected over a 14-month period, but there were significant fluctuations in the estimate of error. The standard error of a twelve-rabbit assay of the type described was of the order of 12%.

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QUERIES

57 **QUERY:** The effects of a preservative added to fresh and to wilted alfalfa silage was tried in miniature silos. The lactic acid concentration, measured at various periods after the ensiling date, is given in Table 1. Is the "Remainder" in the table of analysis of variance a valid estimate of error?

TABLE 1

LACTIC ACID (MILLIGRAMS PER GRAM OF SILAGE) AT SUCCESSIVE PERIODS IN ALFALFA SILAGE TREATED IN 4 WAYS

	Fresh		Wilted	
Period	Check	Preservative	Check	Preservative
1	13.4	16.0	14.4	20.0
2	37.5	42.7	29.3	34.5
3	65.2	54.9	36.4	39.7
4	60.8	57.1	39.1	38.7
5	37.7	49.2	39.4	39.7

Analysis of Variance

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Treatment	3	556	185
Period	4	2974	744
Remainder	12	596	49.7

ANSWER: The assumptions underlying the analysis of variance were discussed by Eisenhart in Vol. 3, pages 1–21 of this journal (March, 1947). From an examination of your data, the only serious question appears to be this: Are there interactions between the treatments and the periods of time? If so, two difficulties arise: (i) the meaning of the main effects is restricted; and (ii) the mean square for "Remainder" is larger than the expected value of the real error.

In your sample, it is plain that the curved regressions on time are not the same for fresh silage and for wilted. In the fresh, the curve turns downward at the later periods, while in the wilted it reaches a plateau. I am a bit skeptical as to whether this is characteristic of the population —I do not find it in some other data available. However, for illustration it is worth testing the hypothesis of zero interactions.

On the assumptions that the periods correspond to equal *effective* intervals, the differences corresponding to polynomial regressions of the first four powers are set out in Table 2. For the convenience of the reader, the ξ'-coefficients of Fisher and Yates are appended. As an

TABLE 2
DIFFERENCES FOR FOUR ORTHOGONAL REGRESSION COMPARISONS

Power of Polynomial	Fresh		Wilted	
	Check	Preservative	Check	Preservative
Linear	71.9	80.8	59.8	43.6
Quadratic	−126.5	−79.2	−33.6	−33.2
Cubic	−22.3	4.4	5.4	11.3
Quartic	49.1	−4.6	−1.4	5.1

	Coefficients					Sum of Squares
Linear	−2	−1	0	+1	+2	10
Quadratic	+2	−1	−2	−1	+2	14
Cubic	−1	+2	0	−2	+1	10
Quartic	+1	−4	+6	−4	+1	70

illustrative computation, the quadratic component for the fresh check is

$$2(13.4) - 1(37.5) - 2(65.2) - 1(60.8) + 2(37.7) = -126.5.$$

As is often the case in factorial experiments, it seems reasonable to assume that the cubic and quartic interactions may be estimates of the real error. These are calculated as follows:

$$\frac{1}{10}\left[(-22.3)^2 + \cdots + (11.3)^2 - \frac{(-22.3 + \cdots + 11.3)^2}{4}\right] = 67.31$$

$$\frac{1}{70}\left[(49.1)^2 + \cdots + (5.1)^2 - \frac{(49.1 + \cdots + 5.1)^2}{4}\right] = 26.84$$

The divisors, 10 and 70, are the usual sums of squares of the coefficients in Table 2. The sum of these results, 67.31 + 26.84 = 94.15, divided by the corresponding degrees of freedom, 3 from each comparison, yields the estimate of error, 15.7, about one third of the mean square for "Remainder" in Table 1.

The linear and quadratic effects have the following sums of squares:

$$L = \frac{(71.9 + \cdots + 43.6)^2}{(10)(4)} = 1640$$

$$Q = \frac{(-126.5 - \cdots - 33.2)^2}{(14)(4)} = 1326$$

The remaining sum of squares for "Periods," 2974 − (1640 + 1326) = 8, is negligible. This adds credence to the assumption that the interactions of these effects with treatments are no more than random variation.

The interaction between treatments and linear regression,

$$\frac{(71.9)^2 + \cdots + (43.6)^2}{10} - 1640 = 78,$$

may be partitioned into three comparisons:

$$L \times (F \text{ vs. } W) = \frac{[(71.9 + 80.8) - (59.8 + 43.6)]^2}{(10)(2)(2)} = 60.76$$

$$L \times T = \frac{[(71.9 + 59.8) - (80.8 + 43.6)]^2}{(10)(2)(2)} = 1.33$$

$$\text{Interaction} = \frac{[(71.9 + 43.6) - (80.8 + 59.8)]^2}{(10)(2)(2)} = 15.75.$$

Corresponding interactions and components for the other regressions are calculated in the same way, only the divisor, 10, changing to 14, 10 and then 70 in the successive regressions.

The pertinent main effects and interactions are copied into Table 3.

TABLE 3
PERTINENT PARTS OF ANALYSIS OF VARIANCE

Source of Variation	Degrees of Freedom	Mean Square
Treatments:		
Fresh vs. Wilted	1	533
Other comparisons	2	11
Periods:		
Linear	1	1640
Quadratic	1	1326
Higher degree polynomials	2	4
Interactions:		
Fresh-Wilted × Linear	1	61
Fresh-Wilted × Quadratic	1	345
Others with linear and quadratic polynomials	4	24
Error (Interactions with higher degree polynomials)	6	15.7

The suspected difference between the trends in the fresh and wilted silage shows up in both the linear and quadratic interactions, the latter being especially prominent.

We now have evidence that the mean square for "Remainder" in Table 1 includes population interactions, and is therefore not an unbiased estimate of error. Of much greater interest is the consequence that one cannot draw conclusions about *the* effect of the wilting treatment—the *various* effects of this treatment may differ with the period of storage. At the beginning of the storage period and again at the end the differences are small and non-significant. It is in the third and fourth periods that the differences are most pronounced.

GEORGE W. SNEDECOR

58 **QUERY:** Table 39, page 218, of Fisher's *Statistical Methods for Research Workers*, 8th edition, implies that the expected value of the variance of the subsample means is

$$(1) \qquad A + \frac{B}{k}.$$

When I go through the derivation I find it to be

$$(2) \qquad \frac{n}{n-1} A + \frac{B}{k}.$$

It seems to me that the thing boils down to the definition of the variance of the true population means from which the sub-samples have been drawn. In other words, the difference seems to depend on whether one takes the sum of squares of the true values and divides by n or by $(n - 1)$. My interpretation was, of course, that one computed the variance of the population means by summing the squares of the deviations and divided by n. The results given in (1) seem to be obtained by dividing by $(n - 1)$. This is particularly awkward when n is small, like 2, where the two methods differ by a factor 2. Perhaps you will let me know what you think about this?

ANSWER: The particular formula obtained as the result of a mathematical argument is, as you indicate, dependent on the particular definitions adopted and the mathematical model set out.

It is clear that the expected value of the variance of the subsample means will be

$$A + \frac{B}{k},$$

provided that the expected value of the mean square "Between families" is

$$kA + B.$$

Let the data consist of n families with k observations in each family. Let x_{ij} represent the jth observation in the ith class. Assume that the variability of x_{ij} is attributable to two sources: (i) variability affecting all members of the ith class equally, and (ii) variability peculiar only to that particular observation.

Assume that

$$x_{ij} = m + f_i + e_{ij},$$

where m = population mean value of x_{ij}, f_i = variable changing from

class to class, but constant for all members of a given class, e_{ij} = variable changing from class to class and also from observation to observation. Assume that the population mean values of f_i and e_{ij} are zero, f_i and e_{ij} are independent and are samples from general populations whose variances are A and B respectively.

Summing over the ith class, we obtain

$$T_i = \sum_j x_{ij} = km + kf_i + \sum_j e_{ij} .$$

Then,

$$\text{(a)} \qquad E\left(\frac{\sum_i T_i^2}{k}\right) = nkm^2 + nkA + nB.$$

Also,

$$\frac{\sum_i T_i}{nk} = \frac{1}{nk}\left(nkm + k\sum_i f_i + \sum_i\sum_j e_{ij}\right),$$

And

$$\text{(b)} \qquad E\left[\frac{(\sum_i T_i)^2}{nk}\right] = nkm^2 + kA + B.$$

Now, the sum of squares among families is,

$$\frac{\sum_i T_i^2}{k} - \frac{(\sum_i T_i)^2}{nk},$$

and the expected value of the mean square among families is

$$\text{(c)} \qquad E\left[\frac{1}{n-1}\left\{\frac{\sum_i T_i^2}{k} - \frac{(\sum_i T_i)^2}{nk}\right\}\right]$$

$$= \frac{1}{n-1}\left[E\left(\frac{\sum_i T_i}{k}\right)^2 - \frac{E(\sum_i T_i)^2}{nk}\right].$$

Substituting from (a) and (b) in (c), we have

$$\text{(d)} \qquad \frac{1}{n-1}\left[E\left(\frac{\sum_i T_i^2}{k}\right) - \frac{E(\sum T_i)^2}{nk}\right]$$

$$= \frac{1}{n-1}\left[nkm^2 + nkA + nB - nkm^2 - kA - B\right]$$

$$= kA + B.$$

T. A. BANCROFT

ABSTRACTS

44 HARSHBARGER, BOYD. (Virginia Agricultural Experiment Station.) **Triple Rectangular Lattices.**

The paper presented an extension of the Rectangular Lattices which was published as Memoir 1 by the Virginia Agricultural Experiment Station, to the case where there are three groups. All formulas necessary for the Triple Rectangular Lattice are given.

45 BLISS, C. I. and JACKMAN, M. C. (Connecticut Agricultural Experiment Station.) **Estimation of the Mean and Its Error from Incomplete Poisson Distributions.** *Published in Bulletin No.* 513, *Connecticut Agricultural Experiment Station, January,* 1948.

When organisms or events occur at random in space or time the number of individuals in each unit follows the Poisson distribution. It may be necessary or convenient to record in full only the units containing few observations such as 0, 1, 2 and 3, combining the rest into a single category. Tables have been computed to facilitate the estimation of the population mean and its standard error from such incomplete counts. Agreement of the observed frequencies with those expected by the Poisson distribution can be tested readily by χ^2. The calculation of these statistics is illustrated by haemocytometer counts for measuring the density of the spores of milky disease in the blood of an infected Japanese beetle larva.

46 BERKSON, JOSEPH. (Division of Biometry and Medical Statistics, Mayo Clinic, Rochester, Minnesota.) **Comparison of Mean-Cost-Rating and the Biserial Correlation Coefficient.**

The mean-cost-rating as previously defined can be estimated conveniently and with sufficient accuracy for many practical purposes in the cases in which the measurement is normally distributed, by plotting the observed *utility* against *cost* on normal-normal paper. A line is fitted to these points by eye or according to the formula previously given in terms of the means and standard deviations of the measured variate. The values of the *cost* are read off for utilities, 0, 0.05, 0.10, 0.15, $\cdots$, 0.95, 1.00, and from these the mean-cost is calculated by the trapezoidal rule.

A comparison was made, for some actual series, of the mean-cost-rating so obtained and the biserial correlation coefficient. The results were inconclusive in respect to any generalization regarding the relation between the two.

47 BERNSTEIN, MARIANNE E. (Syracuse University.) **"Use of Statistical Methods in Human Genetics." Test for Monomeric Inheritance Involving Four Alleles.** *Part of a paper to be published in "Journal of Heredity."*

Danforth (1921) stated that individuals vary as to the presence, absence and distribution of hair on the middle segments of the fingers and showed that complete absence is a recessive trait. This author offers a monomeric-multiple allele hypothesis to explain the distribution of hair, calling the alleles (in order of increasing dominance) A_0, A_1, A_2, and A_3, the subscripts denoting the number of fingers affected.

The hypothesis was tested on sibling pairs using Cotterman's formula by which the expected ratio of both siblings dominant to both siblings recessive is:

$$\frac{p(4 + 5p - 6p^2 + p^3)}{(1 - p)^2(2 - p)^2} \qquad \text{where } p = 1 - (\%\text{ recessives in sample})^{1/2}$$

Chi-square between observed and expected ratios varied between .047 and .951 with one d.f.

In matings of two dominants the percentage of recessive children expected is

$$\left(\frac{q}{1 + q}\right)^2$$

where $q = 1 - p$. Though the proposed monomeric mode of inheritance involves four gene substitutions, the above formulae developed for two gene substitutions could be employed by a grouping process as follows:

Phenotype of Matings Dominant --- Recess	Recessive offsprings Obs.	$N\left(\frac{q}{1 + q}\right)^2$	Nq^2 Random	N
A_3 --- A_2, A_1, or A_0	6	8.2	27.6	40
A_3 or A_2 --- A_1 or A_0	11	10.3	20.4	48
any hair --- no hair	14	18.3	47.4	114

48 RASHEVSKY, N. (The University of Chicago.) **Recent Advances in Mathematical Biophysics.** *Symposium on Mathematical Biology.*

A general review of the field of mathematical biophysics is given. Examples of agreement between theoretical deductions and experimental data are given, such as cell division, cell respiration, incidence of cancer with age, reaction times, psychophysical discrimination, discrimination of intensities and measurement of aesthetic values of visual patterns.

The paper covers essentially the content of the author's article, "Mathematical Biophysics," (*Medical Physics*, edited by Otto Glasser, page 706, Yearbook Publishers, Inc., 1944).

49 BRANSON, HERMAN. (Howard University.) **On the Theory of Metabolizing Systems with Especial Reference to the Use of Isotopic Tracers.** *Symposium on Mathematical Biology.*

A mathematical treatment of metabolizing systems is outlined which describes some important characteristics of such systems in terms of a rate function and a metabolizing function. The resulting integral equations are applied to several problems of biological and chemical interest. The equations are solved with functions derived from several sets of available data. Experimental procedures for determining the functions are discussed. The integral equations are shown to be valuable in problems employing isotopic tracers. Evidence is presented to support the view that this integral equation formulation may be a convenient means of correlating and integrating some of the work now being done with tracer molecules in biological systems.

Some of the material discussed in this paper has been published in *The Bulletin of Mathematical Biophysics*, 9, 93, 1947.

50 OPATOWSKI, I. (University of Michigan.) **Mathematics in Radiobiology.** *Symposium on Mathematical Biology.*

An attempt is made to interpret the carcinogenic action of radioactive substances on the basis of a mechanism which is a combination of the following ideas: the idea of P. Jordan of an extraneous molecule reaching a particular body molecule in a random fashion to induce a macroscopic biological event; the idea of an intermediate substance as a more direct cause of the cancer; and the idea of the growth of the cancer from a microscopic malignant center. The theory succeeds in describing a part

of the result achieved by A. M. Brues, H. Lisco and M. Finkel through the induction of bone sarcoma in mice by Sr^{89}.

51 LANDAHL, H. D. (The University of Chicago.) **Mathematical Theory of Discrimination and Conditioning.** *Symposium on Mathematical Biology.*

The mathematical theory of discrimination and conditioning is discussed and applications of the theory to experimental data are illustrated by several examples.

The paper covers essentially the contents of Chapters IX and XI of A. S. Householder and H. D. Landahl's *Mathematical Biophysics of the Central Nervous System.* (Principia Press, 1945).

52 CULBERTSON, JAMES T. (The University of Chicago.) **Mathematical Theory of Perception.** *Symposium on Mathematical Biology.*

This paper describes a mechanism for (1) bottle-neck optic nerve conduction and (2) the recognition of visual spatial forms. (1) In this mechanism the w retinal receptor neurons are in one-one causal relation to a set D of w central neurons, the connecting optic-nerve containing less than w fibers. (2) Also a set ϕ of μ spatial forms (herein defined) is in the one-one causal relation to a set F of μ central neurons so that if f_i (any given number of F) fires, then the corresponding ϕ_i has occurred in the retinal image. Only ϕ_i can fire f_i, but f_i may fire for any position, size or orientation of ϕ_i on the retina, with the restriction that ϕ_i not be smaller than a minimum size, which is a function of retinal position. Neuron economy is considered throughout.

This paper is published in *The Bulletin of Mathematical Biophysics*, 10, 31, 1948.

53 RAPOPORT, ANATOL and ALFONSO SHIMBEL. (The University of Chicago.) **Suggested Experimental Procedure for Determining the Satisfaction Function of Animals.** *Symposium on Mathematical Biology.*

Some general experimental procedures are suggested to test a previously developed theory of motivation interactions which gives a quantitative description of factors in motivation. The experiments are devised

with a view of varying simultaneously the "positive" and "negative" terms of a postulated satisfaction function which is supposed to depend on the subject's "effort" and "remuneration." If the output of effort on the part of the subject reaches a steady state for a given set of conditions, this output is taken to be the optimum output under those conditions. In other words, it is supposed that the satisfaction function is "maximized". From the equations describing the derivatives of the satisfaction function with respect to different variables, the "biological constants" of the individual can be computed and his behavior predicted under a variety of other conditions. In particular, on the basis of previous papers, it should be possible to predict the behavior of two "cooperating" and "sharing" individuals.

This paper is published in *The Bulletin of Mathematical Biophysics*, 9, 169, 1947.

54 SMITH, ROBERT E. (Naval Medical Research Institute) and MANUAL F. MORALES (The University of Chicago.) **Theoretical Studies on Blood-Tissue Exchange of Inert Solutes.** *Symposium on Mathematical Biology.*

Following a brief review of the kinetics of inert gas uptake by composite tissue regions as previously developed by the authors, there is made a comparison between this fairly inclusive formulation and other, simpler formulations, of which Von Schrotter's is the fundamental prototype. It is shown analytically that the Von Schrotter formulation gives a satisfactory asymptotic approximation to the more complete theory whenever, (1) it can be assumed that for each tissue the product of the area of its exchange surface and the permeability of said surface is much greater than the blood flow to the tissue, (2) the average gas concentration in the blood volume is near the venous concentration, and (3) the tissues are arranged in "distinct parallel". It is concluded that especially the first of these approximations cannot be made with any assurance on the basis of existing experimental data.

55 HEARON, JOHN Z. (The University of Chicago.) **The Kinetics of Blood Coagulation.** *Symposium on Mathematical Biology.*

The overall process of the production of fibrin from fibrinogen is considered to occur in two distinct, consecutive phases: (a) the formation

of thrombin, T, from prothrombin, P, by the action of "active" thromboplastin, Th', and (b) the conversion of fibrinogen, F, to fibrin by the action of thrombin. The system is examined kinetically on the basis of the following reactions which accord to Th', P, T and F the required roles and include the action of calcium:

$$Th + Ca^{++} \rightleftharpoons Th'$$

$$Th' + P \rightleftharpoons Th' \cdot P$$

$$Th' \cdot P \rightleftharpoons Th' + T$$

$$T + F \rightleftharpoons T \cdot F$$

$$T \cdot F \longrightarrow T + fibrin$$

The rate of the process is formulated in terms of the concentrations of the above constituents. The rate expression may be integrated under the assumption of a steady state which may be justified on the basis of the irreversibility of the last step and recent data of Ferry et al which indicates that T is "carried down" with the fibrin clot and that the ultimate restitution of T to the system is slow relative to the primary clotting process. In this manner there is obtained an equation for the so called prothrombin time, when the initial conditions are specified as being those which obtain for the clinical determination of prothrombin. The variation of the prothrombin time, t_a, as a function of P and Th, predicted from the analysis is compared to experimental data. The results are discussed with particular reference to the plasma dilution curves used in the clinical determination of P and the influence of various factors such as the potency of the Th preparation employed. Specifically from the expression for $t_a = f(P, Th, Ca^{++})$ the plasma dilution giving a specified uncertainty in t_a may be determined, and a linear plot is obtainable. The parameters of straight line may be employed as a numerical index to the potency and permit construction of accurate plasma dilution curves from a minimum number of points. The availability of the expression for t_a makes possible the critical examination of many empirical procedures already in practice. Further, certain of such procedures may now be carried out analytically.

This paper will be published in *The Bulletin of Mathematical Biophysics*, September, 1948.

LOTKA, ALFRED J. (Statistical Bureau, Metropolitan Life
56 Insurance Company.) **The Physical Aspect of Organic Evolution.** *Symposium on Mathematical Biology.*

The system made up of a number of component species of living organisms and their inorganic environment has evolved and continues to evolve under a stream of available energy from the sun. The differential survival of the several components depends on the degree of the success of each in the competition to secure its share of the available energy from this stream.

Analytically, the problem of organic evolution presents itself as the study of the distribution and redistribution of matter, as a function of time, among specified components of the system of nature.

Physically, the problem is to investigate the relation of this distribution and redistribution to the physical properties of the components and their energy environment.

This type of problem is familiar from the study of physicochemical systems, in which the distribution and change in distribution of matter among specified components (elements, compounds, phases) is examined in its relation to parameters of state (volume, pressure, temperature, etc.). But, whereas it is characteristic of a large part of the domain of physicochemical dynamics that structure and mechanism play at most a subordinate role, in the study of organic evolution the structural and mechanical properties in terms of which the components must be specified, and on which their aptitude for capturing energy depends, play the dominant role.

Inasmuch as each component seeks to enlarge its own share of the available matter and energy, and since they cannot each monopolize the whole, the question arises, what is the collective result of their competitive activities? It is in terms of this collective result that we must expect to find the law of organic evolution expressed.

This paper will be published in *The Bulletin of Mathematical Biophysics*, September, 1948.

MORALES, MANUEL F. and D. JEAN BOTTS (The Univer-
57 sity of Chicago) and TERRELL L. HILL (University of Rochester.) **On the Statistical Mechanics of Antibody-Antigen Combination.** *Symposium on Mathematical Biology.*

Employing T. Teorell's model, there are derived equilibrium statis-

tical equations for the reactions between antibody (A) and antigen (G), $A + A_i - 1 \rightleftarrows A_iG$; $i = 1, 2, \cdots n$, where n is the antigen "valence". Four hypotheses are considered: (I) The free energy of bonding of a single A on a reactive site of G is independent of the state of the remaining sites of G. (II) There is an energy of interaction, E_{AA}, between A's bonded to the same G in such a manner that they are nearest neighbors on the lattice of G sites.[1] (Three regular lattices are treated, corresponding to the contact points on any sphere in the cubic and hexagonal closest packing of spheres and in the simple cubic packing of spheres). (III) The effect of A binding on the translational and rotational properties of the $A - G$ aggregate are taken into account assuming that both A and G are spherical molecules of approximately the same radius. (IV) The effects treated under (II) and (III) are combined. In each of the foregoing cases it is shown how the equilibrium constants of the reaction system may be obtained from experimental concentration measurements. Numerical calculations are given to show that the perturbations, (II), (III), and (IV), lead to considerably different results than the simple treatment corresponding to case (I).

58 SHIMBEL, ALFONSO, and ANATOL RAPOPORT (The University of Chicago.) **A Statistical Approach to the Theory of the Central Nervous System.** *Symposium on Mathematical Biology.*

A "probabilistic" rather than a "deterministic" approach to the theory of neural nets is developed. Neural nets are characterized by certain parameters which give the probability distributions of different kinds of synaptic connections throughout the net. Given a "state" of the net (i.e., the distribution of firing neurons) at a given moment, an equation for the state at the next moment of quantized time is deduced. Certain very special cases involving constant distributions are solved. A necessary condition for a steady state is deduced in terms of an integral equation, in general non-linear.

Published in *The Bulletin of Mathematical Biophysics*, 10, 41, 1948.

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[1] A portion of this work will appear in *The Journal of Chemical Physics*, May, 1948.

THE BIOMETRIC SOCIETY

There is a fine old "saw", no doubt duplicated in the language of every country in which the Society has members, to the effect that the shoemaker's child is always without shoes. And, what the Biometric Society needs is a statistician. Data, concerning the membership, there is in abundance but it doesn't add up to a nice round number. Therefore, without benefit of analysis, may we report some "vital" information, but, please, no letters to the editor that "the given numbers don't seem to check", or "the number of charter members varies by a few" at some later date. The entire world may have been drawn close, even too close, but it still takes considerable time to smooth out all details over distances of thousands of miles.

By the last of April there were 528 paid members, 370 of them charter. This number does not include 51 registered members still involved in exchange difficulties. The grand total of 579 included 166 representing 24 countries other than Canada, Mexico and the United States. Eighty-one of these are members of the British Region, including a few from Scotland and Ireland as well as England. Australia is represented by twenty-three; France by eighteen; Italy by eleven; South America by seven from Argentina, Brazil, Peru and Venezuela; India and Switzerland by four each; Holland and Sweden by three each; Hawaii and Norway by two each; and China, Czechoslovakia, Denmark, Malaya, the Philippines, Portugal, Puerto Rico and Trinidad in the British West Indies by one each.

Any young organization, during its growing pains, is apt to need some financial assistance and the Biometric Society is no exception. It was soon evident that the duties of the Secretary's office could not be handled without an executive assistant and some office equipment, nor could the membership be increased to the point of supporting an organization without some help in the early stages. Officers of the Rockefeller Foundation, which aided in the organization last September at Woods Hole, were sympathetic to a proposal for supplementary funds to help carry out successfully the objectives of the Society. On March 1, 1948, the Foundation very generously granted a fund "not to exceed $7,400, or as much thereof as may be necessary, to Yale University for the support of the Biometric Society for the period ending February 28, 1951."

The University has now received $4,000 to cover expenditures during the first year under the terms of the grant. Because the tax status of the Society cannot be established for a year, Yale University agreed to receive the funds for disbursement on order of the Society.

The grant was made on the basis of providing a part-time assistant for the Secretary's office, the purchase of necessary office furniture and supplies, and to cover printing, postage, and publicity for promotion. Further, the money is to aid in arranging for and financing international conferences as well as regional meetings, and in maintaining a suitable journal. *Biometrics* was selected by the Council as the journal which at present suits the needs of the Society.

Mrs. John H. Watkins, who has been acting informally since last November, has been appointed Executive Assistant. Yale University has offered office space, rent-free, as soon as it becomes available. Until that time the Watkins' are letting us use their home as a temporary office and have given space for the furniture and equipment.

Only two regions have been formally established. The British Region held an inaugural meeting at University College, London, on April 29, 1948, to adopt a set of rules and make formal arrangements for conduct of the Region's affairs. Professor R. A. Fisher, President of the Society and Dr. J. W. Trevan, Vice-President for the British Region, addressed the meeting.

Charles P. Winsor, Vice-President of the Eastern North American Region, has appointed the following committees for the year: Program committees to cooperate with

1. The A.A.A.S.: Kenneth S. Cole, D. B. DeLury, M. Demerec, N. Rashevsky, G. G. Simpson and W. H. Youden, chairman.
2. The A.S.A.: Churchill Eisenhart, H. C. Fryer, Oscar Kempthorne, P. J. Rulon, W. R. Thompson and H. W. Norton, chairman.
3. The A.P.H.A.: H. L. Dunn, Margaret Merrell, Jane Worcester and Hugo Muench, chairman.
4. Federation of American Societies of Experimental Biology: E. J. deBeer, H. K. Hartline, Lloyd Miller and C. I. Bliss, chairman.

A French and a Benelux Region were approved by the Council in 1947, but neither has as yet completed organization. Adriano Buzzati-Traverso, a member of the Council, wrote late in February that "epistolary discussion is under way between Professor Georges Teissier", also a Council member, and himself "in order to make definite proposals to establish a Region, which should include members of the Society of

France, Italy, Switzerland, and eventually the Benelux Region." Professor Teissier wrote the last of April that he expects to see the Italians, who are anxious to join a regional group, at Stockholm and at Paris during the Genetical and Zoological Congresses. He adds that if the start is a little slow, "les choses ne vont néanmoins pas trop mal."

Organization is going forward on the Australian Region with a plan that one person in each of various cities organize local groups which will meet at intervals. These group organizers with M. H. Belz, a member of the Society Council, will constitute an Australian Regional Council. Thus far the city representatives are E. A. Cornish, officer-in-charge, Section Mathematical Statistics, Council for Scientific and Industrial Research, and lecturer in mathematical statistics at the University of Adelaide, for Adelaide; Rupert Leslie, Section Mathematical Statistics, CSIR, attached to Division of Forest Products, for Melbourne; and Helen N. Turner, Section Mathematical Statistics, CSIR, attached to Division of Animal Health and Production and lecturer in Veterinary Biometry, University of Sydney, for Sydney.

R. A. Fisher, President of the Society, was one of two foreign associates elected at the annual meeting of the National Academy of Sciences.

The Secretary's office has received copies of *Ciencia e Investigación*, published in Buenos Aires, *Tydschrift voor Sociale Geneeskunde*, *The American Statistician* and the *Statlab Review* of Iowa State College which contain accounts of the Society's organization. Other journals containing such accounts, or reprints from them, will be appreciated in order to keep as complete a publicity file as possible.

NEWS AND NOTES

The University of Michigan Summer Session (Ann Arbor) will offer a special four weeks session in survey research methods. The program will include introductory and advanced courses in survey research and sampling methods as well as a course in methods of statistical analysis. The survey research course will cover study design, questionnaire construction, interview technique, coding methods and related material. The staff will include **Rensis Likert, Angus Campbell, Charles Cannell, Roe Goodman, George Katona, Daniel Katz, Leslie Kish, Eleanor Maccoby,** and **Charles Metzner** of the staff of the Survey Research Center. **Morris Hansen, William Hurwitz** and **Benjamin Tepping** of the Bureau of the Census will offer the advanced sampling courses. Other special lecturers will participate in the program. All courses will be given July 19 through August 13, 1948. The introductory course in survey methods is being offered June 21 to July 17. All courses are offered for graduate credit and students must be admitted by the Graduate School.

CHINA—**Wang Chien-ming,** College of Agriculture, Sun Yat-Sen University, Canton, writes: "During the second world war we have been robbed of quite a number of textbooks, reprints, bulletins and other periodicals. I think you may take it as a pleasure to cooperate with us by sending publications in connection with statistical treatment of biological assays, biometry and field technique."

ENGLAND—**K. A. Brownlee,** Research and Development Department, The Distillers Company, Ltd., Great Burgh, Epsom, Surrey, finds that much the greater part of his work is devoted to the field of biometrics. The Company runs a number of fermentation processes and the usual tests of significance are desirable for analysing process data. Along the lines of biological assay, they have greatly increased the accuracy of the plate-cup assay for penicillin and streptomycin by the use of a doubly confounded layout. For some large scale experiments, particularly on the manufacture of penicillin, they have used factorial designs, generally with confounding, and sometimes fractionally replicated. . . . **D. J. Finney,** lectureship in the design and analysis of scientific experiment, University of Oxford, has actively contributed to the development of *Biometrics*. He states, "I think the journal is very well worthwhile, and the first number of Volume 3, I find particularly useful. The only suggestion I have to make is that the column of social gossip be abandoned." This is the second time such a suggestion has been received during the last three years. Do the rest of our readers

feel the same about "News and Notes"? . . . **J. B. S. Haldane,** University College, London, Gower Street, writes, "I am just trying to do some biometry on Ethinocardium, which is about the only solid box other than the human skull on which large numbers of measurements have been made. It looks as though one would have to apply the Thurstone type of analysis to it." . . . **I. B. Perrott,** 17 Widney Manor Road, Solihull, Birmingham, a mathematician and statistician at Leicester College of Technology, lectures to advanced students. He is interested in mathematical statistics in general, and in the design of experiments in particular. Mr. Perrott has worked on the incidence of certain diseases in various industries. As a statistical consultant, he advises senior research scientists (physicists, chemists and biologists) on the design of their experiments and assists with the analysis of the results. . . . **E. C. Wood,** Virol Limited, Hanger Lane, Ealing, is to give a talk on "Statistical aspects of chemical analysis" the first of June at the Netherlands Chemical Society, International Congress in Utrecht, (Holland).

FRANCE—**R. Fortet**, in the faculty of science at the University of Caen (Calvados), has joined the Biometric Society. His field of specialization is probability theory, more particularly Markoff chains and stationary stochastic processes. He writes, "I am interested in your Society and its review."

NORWAY—From the Agricultural College of Norway, Vollebek, **Oivind Nissen** attended the Plant Breeding Conference January 26-30, 1948 at Raleigh, North Carolina. He is a plant breeder who is working on forage species, primarily clover and timothy. During a second visit on March 9, Mr. Nissen gave an illustrated seminar talk on plant breeding in Norway. . . . From the same College comes word from a charter member of the Biometric Society, **Per Ottestad.** In 1931 he was appointed assistant in the research institute (marine biology) of Professor Hjort and was occupied with biological research. He states, "Gradually I became interested in statistics because I began to understand that this science was necessary for the development of biological research." In 1937 he was appointed assistant professor of mathematics at the Agriculture College. "Our students are not trained in calculus and, therefore, it is not possible to explain to them how the various theorems have been deduced mathematically. I try to explain the fundamental logical principles of statistics by means of examples and exercises. Experimental design is no general subject for teaching in our college. We are now working with a revision of the curriculum, and the idea is to introduce a course on general scientific methods such as classification, deduction and induction, analysis and synthesis, and experimental design."

PHILIPPINES—**Vincente Mills,** Tuguegarao Branch Office, U. S. Philippine War Damage Commission, Cagayan, sends this encouraging message, "I believe the International Biometric Society is the organization which can effect most successfully the systematic and progressive development of biometry." The U. S. Philippine War Damage Commission is rehabilitating the country from the ravages of war, for which purpose the Congress of the U. S. has authorized the appropriation of five hundred twenty million dollars for compensation of private and public claims. The Commission is under the leadership of **Frank A. Waring,** Chairman, and the Commissioners **Francisco A. Delgado** and **John A. O'Donnel.** Mr. Mills hopes that by the time their task at economic reconstruction shall have been completed, he will have sufficient qualitative facts and quantitative data to be of value in subsequent economic and econometric studies. As Assistant Census Commissioner for the 1939 Census of the Philippines, Mr. Mills became interested in the problems on population, mortality, morbidity, and other biostatistical data.

VENEZUELA—**Eric Michalup,** Actuary, Caracas, writes that he read with great interest the short paper by **Margaret Merrell,** Volume 3: 129–136, 1947 of *Biometrics.* We appreciate your suggestions which have been followed. It would be most helpful if more of our readers would take time to say what you want. Our efforts to secure articles being requested have not been very successful, but we can keep on trying.

UNITED STATES—**Robert A. Harte**, Chief Research Chemist, The Arlington Chemical Company, Yonkers, New York, is particularly interested in allergy. He writes, "There are many problems in allergy which call for statistical handling and we have quite a list of projects which we should like to undertake. An extremely interesting application of statistical methodology to allergy has been initiated in two papers by **T. G. Andrews** (*Journal of Allergy* 14: 322, 1943; 19: 43, 1948) in which factorial analysis has been applied to the responses of a relatively large group of individuals to skin reactions." . . . **Jerome C. R. Li,** Assistant Professor of Mathematics, Oregon State College, Corvallis, is doing teaching and consultant work in statistics. He has started a sequence of two statistics courses for the agricultural students. Computing facilities have been provided for student use. He writes, "The Climate is excellent. Definitely there is the possibility of further expansion in our statistics program." . . . **H. M. C. Luykx**, New York University, College of Medicine, is interested in the application of statistical methods in medicine and public health. More articles demonstrating the value of statistical tools are welcome. . . . **Sophie Marcuse**, formerly statistician

with the Bureau of Human Nutrition and Home Economics is now with the Naval Research Laboratory. She is still in Washington and writes, "The material is different but again it is design that is important in experimentation." . . . **M. B. Mittleman,** Management Counsel of M. B. Mittleman Associates, New Rochelle, New York, calls himself an avocational biometrician. He writes, "For the past 12 years I've been an avocational herpetologist (majored in Zoology at Ohio University). For perhaps the first half of these years, I was vaguely unhappy about the crudity of the taxonomic efforts of myself and others. Having pulled about the same number of taxonomic boners as my colleagues, I felt that herpetology should not be any less amenable to refinement than the other classificatory sciences. **Laurence M. Klauber's** papers provide a tour de force of applied biometrics, and I have found them stimulating and provocative." Mr. Mittleman reports that his vocational application of statistics is in such fields as marketing forecasts and performance analysis. . . . **Max Shiffman**, a member of the faculty of the department of graduate mathematics at New York University, will join the Stanford faculty in September as Professor of Mathematics. During the war he was a research mathematician with the Office of Scientific Research and Development. . . . **George W. Snedecor**, President of the American Statistical Association and visiting Research Professor of Statistics at Alabama Polytechnic Institute, addressed a joint session of the following sections: Biology and Medical Science, Industry and Economics, and the Social Sciences, on the subject, "Increasing the Efficiency of Sampling Investigations," at a recent meeting of the Alabama Academy of Science. . . . **Francis Joseph Weiss,** Special Research Consultant, Sugar Research Foundation Inc. states, "I am looking forward to having, through your Biometric Society, closer contact with biologists and biochemists who like me are interested in the mathematical presentation of biological phenomena." . . . **H. G. Wilm** formerly with the Rocky Mountain Forest and Range Experiment Station at Fort Collins, Colorado, is now with the Southern Forest Experiment Station with headquarters at New Orleans, Louisiana. He will conduct flood-control survey work in the Forest Service's Southern Region and adjacent territory, covering an area which extends in general from east Texas to the south Atlantic Coast. A part of his job will be adapting and applying sampling techniques and other statistical methods to flood-control surveys.